Substituted 1-(Aminomethyl)-2-(arylacetyl)-1,2,3,4-tetrahydroisoquinolines: A Novel Class of Very Potent Antinociceptive Agents with Varying Degrees of Selectivity for κ and μ Opioid Receptors

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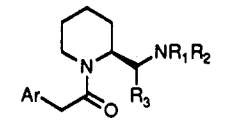
This study describes the synthesis of a series of novel substituted 1-(aminomethyl)-2-(arylacetyl)-1,2,3,4-tetrahydroisoquinolines, and discusses their structure–activity relationships (SARs) using binding affinity for opioid receptors and antinociceptive potency as the indices of biological activity. The introduction of a hydroxy substituent in position 5 of the isoquinoline nucleus generated a compound, **40**, which is 2 times more potent than the previously disclosed unsubstituted analogue **39** in mouse models of antinociception. A QSAR analysis of the 5-substitution clearly demonstrates that antinociceptive activity is inversely associated with the lipophilicity of the substituents. The substituted compounds described herein are less selective for the κ opioid receptors than the unsubstituted isoquinoline **39**. For example, the 5-hydroxy-substituted compound **59** shows high affinity for κ opioid receptors (K_i κ = 0.09 nM) and a K_i μ/K_i κ ratio of only 5. However, a multiple linear regression analysis demonstrates a lack of correlation between antinociceptive activity and affinity for the μ opioid receptor. On the other hand, the correlation between binding affinity to κ opioid receptor and antinociceptive activity was statistically significant.

Introduction

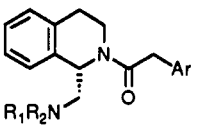
κ opioid agonists produce a variety of pharmacological effects including antinociception in animals and analgesia in man.[1] Since selective κ opioid agonists are devoid of the well-known side effects associated with morphine-like analgesics (which act via μ receptor activation) there has been considerable interest in recent years in identifying and developing such a compound as an effective and safe pain relieving agent.

Previous studies have shown that the condensation of a benzene ring in C_3–C_4 position of the piperidine nucleus of certain 1-(arylacetyl)-2-(aminomethyl)piperidine derivatives (**1**)[2] produces a novel class of κ opioid receptor agonists, **2**, with increased antinociceptive activity.[3] This modification was prompted by the hypothesis that aromatic groups, in non-peptidic opiates, may mimic Tyr[1] and/or Phe[4] of the N-terminal residue of opioid peptides.[4,5] Tyr[1] is easily recognizable in the pharmacophore of alkaloid analgesics and is thought to carry the "message" for opioid receptor activation.[6] In order to mimic more closely the structure of the Tyr[1] moiety, a hydroxy group has now been introduced in all the positions of the condensed benzene ring of tetrahydroisoquinolines **2**. In addition, different substituents have been introduced in that position of the isoquinoline nucleus shown to be associated with maximal potency with an OH substituent, generating compounds of general formula **3a**.[7]



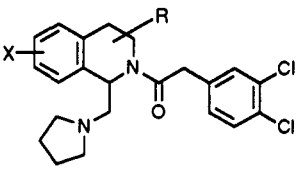
1

Ar = substituted phenyl
R_1,R_2 = linear or cyclic alkyl
R_3 = H, Me



2

Ar = substituted phenyl
R_1,R_2 = linear or cyclic alkyl



3a: X = OMe, OH, $(OH)_2$, Me, SMe, Cl, F
R = H
3b: X = H
R = Me, Me_2

Furthermore, we have studied the influence on antinociceptive activity and binding affinity of selected conformational modifications of the pharmacophoric torsional angle, formed between the amidic and basic nitrogens. These conformational modifications have been obtained with the introduction of methyl(s) and *gem*-dimethyl substituents in the piperidine nucleus of the tetrahydroisoquinolines **2**, affording compounds of general formula **3b**.[7,8]

The antinociceptive activity of the compounds has been determined using the mouse abdominal constriction and tail-flick tests following subcutaneous administration. For enantiomers of particular interest, binding affinities to κ, μ, and δ opioid receptors have also been determined. The antinociceptive activity of these enantiomers was also determined using the mouse hot-plate test following subcutaneous administration.

The present paper describes the synthesis and discusses the SAR of a class of substituted 1-(aminomethyl)-2-(arylacetyl)-1,2,3,4-tetrahydroisoquinolines of general formula **3a** and **3b**. In addition, the correlation between κ and/or μ opioid receptor affinity and antinociceptive potency has been examined for these compounds and for

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(6) Portoghese, P. S.; Sultana, M.; Takemori, A. E. Design of peptidomimetic δ opioid receptor antagonists using the message-address concept. *J. Med. Chem.* **1990**, *33*, 1714–1720.
(7) Vecchietti, V.; Giardina, G. Isoquinoline derivatives and their use as analgesics. European Patent EP 0330360 (30.08.89, Lo. Zambeletti SpA). *Chem. Abstr. 112*, 178704b.
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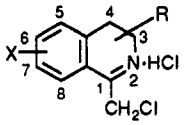
Table I. Physical Properties of Compounds of General Formula 5a and 5b



compd	R	X	formula	mp, °C	anal.	yield, %	recryst solvent	80-MHz ^{1}H NMR, δ (ppm) ($CDCl_3$)
7	H	5-OMe	$C_{11}H_{12}ClNO\cdot HCl$	142–144	C,H,N,Cl	53	EtOAc	7.3–8.1 (m, 3 H), 5.2 (s, 2 H), 4.0 (t, 2 H), 3.2 (t, 2 H)[a]
8	H	6-OMe	$C_{11}H_{12}ClNO\cdot HCl$	127–129	C,H,N,Cl	72	Me_2CO	8.1–8.2 (d, 1 H), 7.1–7.2 (m, 2 H), 5.3 (s, 2 H), 3.9 (t, 2 H), 3.1 (t, 2 H)[a]
9	H	7-OMe	$C_{11}H_{12}ClNO\cdot HCl$	138–141	C,H,N,Cl	64	Me_2CO	7.1–8.0 (m, 3 H), 5.3 (s, 2 H), 3.9 (t, 2 H), 3.1 (t, 2 H)[a]
10	H	5,6-$(OMe)_2$	$C_{12}H_{14}ClNO_2\cdot HCl$	208–211	C,H,N,Cl	32	Me_2CO	7.8 (d, 1 H), 7.0 (d, 1 H), 5.1 (s, 2 H), 4.0 (s, 3 H), 3.9 (t, 2 H), 3.8 (s, 3 H), 3.1 (t, 2 H)[a]
11	H	5-Me	$C_{11}H_{12}ClN\cdot HCl$	172–174	C,H,N,Cl	78	Me_2CO	7.3–8.0 (m, 3 H), 5.3 (s, 2 H), 4.1 (t, 2 H), 3.2 (t, 2 H)
12	H	5-SMe	$C_{11}H_{12}ClNS\cdot HCl$	133–137	C,H,N,Cl	24	Me_2CO	[b]
13	H	5-Cl	$C_{10}H_9Cl_2N\cdot HCl$	194–196	H,N;C,Cl[c]	67	Me_2CO	7.5–8.0 (m, 3 H), 5.2 (s, 2 H), 4.1 (t, 2 H), 3.3 (t, 2 H)[a]
14	H	5-F	$C_{10}H_9ClFN\cdot HCl$	181–184	H,N;C,Cl[d]	69	Me_2CO	7.7–7.9 (m, 1 H), 7.4–7.6 (m, 2 H), 5.3 (s, 2 H), 4.1 (t, 2 H), 3.2 (t, 2 H)
15	3-Me	H	$C_{11}H_{12}ClN\cdot HCl$	169–172	C,H,N,Cl	76	Me_2CO	7.3–8.2 (m, 4 H), 5.3 (s, 2 H), 4.1 (m, 1 H), 3.3 (t, 2 H), 1.4 (d, 3 H)
16	4-Me	H	$C_{11}H_{12}ClN\cdot HCl$	175–178	C,H,N,Cl	89	Me_2CO	7.4–8.2 (m, 4 H), 5.3 (s, 2 H), 4.0 (t, 2 H), 3.2–3.5 (m, 1 H), 1.4 (d, 3 H)
17	3,3-Me_2	H	$C_{12}H_{14}ClN\cdot HCl$	167–170	C,H,N;Cl[e]	21	Me_2CO	7.3–8.2 (m, 4 H), 5.4 (s, 2 H), 3.1 (s, 2 H), 1.6 (s, 6 H)
18	4,4-Me_2	H	$C_{12}H_{14}ClN\cdot HCl$	176–178	C,H,N,Cl	84	Me_2CO	7.3–8.1 (m, 4 H), 5.3 (s, 2 H), 3.8 (s, 2 H), 1.4 (s, 6 H)
19	3,4-Me_2 trans	H	$C_{12}H_{14}ClN\cdot HCl$	146–149	C,H,N;Cl[f]	66	EtOAc	7.3–8.1 (m, 4 H), 5.3 (AB system, 2 H), 4.2 (dq, J = 7.5 and 3.2 Hz, 1 H), 3.1 (dq, 1 H), 1.4 (d, 3 H), 1.3 (d, 3 H)
20	3,4-Me_2 cis	H	$C_{12}H_{14}ClN\cdot HCl$	153–155	C,H,N,Cl	51	EtOAc	7.3–8.1 (m, 4 H), 5.4 (AB system, 2 H), 4.3 (dq, J = 7.5 and 5.4 Hz, 1 H), 3.2 (dq, 1 H), 1.5 (d, 3 H), 1.3 (d, 3 H)

[a] $CDCl_3$ + DMSO. [b] Not recorded. [c] Calcd C, 47.93; Cl, 42.45; found C, 47.02; Cl, 40.79. [d] Calcd C, 51.30; Cl, 30.29; found C, 50.72; Cl, 29.50. [e] Calcd Cl, 29.04; found Cl, 28.38. [f] Calcd Cl, 29.04; found Cl, 27.06.

some selected unsubstituted tetrahydroisoquinolines and tetrahydrothienopyridines.[3]

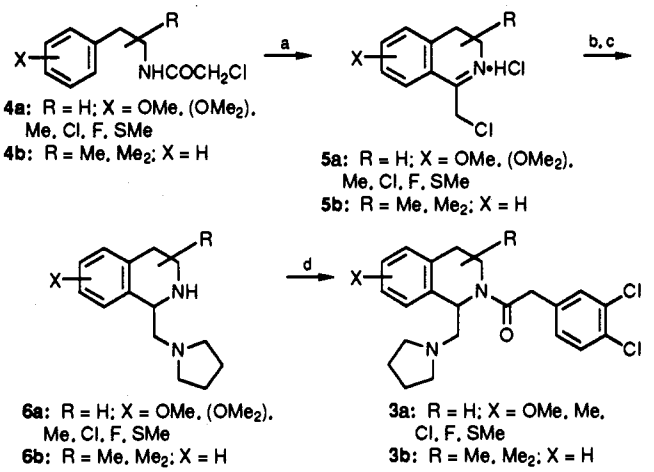
Chemistry

Racemic compounds **40–58** in Table III and IV, of general formula **3a** and **3b**, were synthesized according to Scheme I and II. α-Chloroacetamides of general formula **4a** and **4b**, readily obtained from the corresponding aromatic-substituted ethylamines, were subjected to the Bischler–Napieralsky condensation using P_2O_5 as the condensing agent, in refluxing xylene, to obtain the substituted 1-(chloromethyl)-3,4-dihydroisoquinoline·HCl **7–20**, in Table I, of general formula **5a** and **5b**. Satisfactory yields were found for all the compounds in Table I. Diamines **25–38** in Table II, of general formula **6a** and **6b**, were obtained by treating the activated chloromethyl derivatives with an excess of pyrrolidine in dry MeOH at 0 °C, followed by sodium borohydride reduction of the imine intermediate.

For the monomethyl-substituted compounds **33** and **34**, catalytic hydrogenation of the imine double bond was found to produce almost exclusively the corresponding cis isomer, while reduction with $NaBH_4$ gave both cis and trans isomers in a ratio of about 70:30, respectively. This finding is in agreement with that of Griffith.[9] $NaBH_4$ reduction of the imine intermediate obtained from the 1-(chloromethyl)-3,4-*trans*-dimethyl derivative **19** yielded the diastereoisomeric mixture **37**, containing predominantly the compound where the pyrrolidinylmethyl substituent is in cis relationship with the 4-Me group. The same reduction procedure, applied to the 3,4-*cis*-dimethyl-related diastereoisomer **20** produced the compound **38** in which all three substituents are in cis relationships. No method was found to obtain the diastereoisomer of the 3,4-dimethylisoquinoline with the 1,3- and 1,4-trans geometry (Scheme I).

Diamines **21–24** in Table II of general formula **6c** were obtained from the corresponding methoxy derivatives by refluxing in 48% HBr. Compounds **6a**, **6b**, and **6c** were

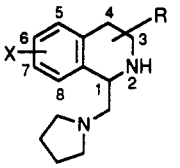
Scheme I[a]



[a] Reagents: (a) P_2O_5, xylene, 140 °C; (b) pyrrolidine, MeOH, 0 °C, 12 h, N_2; (c) $NaBH_4$, MeOH, 0 °C, 3 h; (d) 3,4-$Cl_2C_6H_3CH_2COCl$, K_2CO_3, $CHCl_3$.

(9) Griffith, R. C.; Gentile, R. J.; Robichaud, R. C.; Frankenheim, J. *cis*-1,3,4,6,7,11b-hexahydro-2-methyl-7-phenyl-2*H*-pyrazino-[2,1-*a*]isoquinoline: a new atypical antidepressant. *J. Med. Chem.* **1984**, *27*, 995–1003.

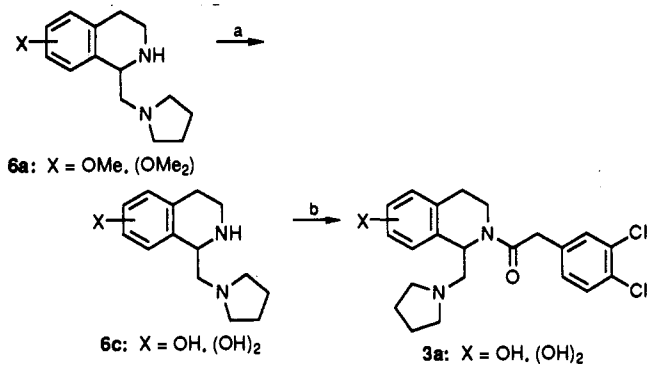
Table II. Physical Properties of Compounds of General Formula **6a**, **6b**, and **6c**



compd	R	X	formula	mp,[a] °C	bp, °C/mmHg	anal.	yield, %
21	H	5-OH	$C_{14}H_{20}N_2O{\cdot}2HBr$	280–281	-	C,H,N,Br	92
22	H	6-OH	$C_{14}H_{20}N_2O{\cdot}2HBr$	226–228	-	C,H,N,Br	93
23	H	7-OH	$C_{14}H_{20}N_2O{\cdot}2HBr$	>200	-	C,H,N,Br	82
24	H	5,6-$(OH)_2$	$C_{14}H_{20}N_2O_2{\cdot}2HBr$	251–252	-	H,N,Br;C[b]	98
25	H	5-OMe	$C_{15}H_{22}N_2O$	-	143–147/0.3	C,H,N	55
26	H	6-OMe	$C_{15}H_{22}N_2O$	-	152–156/0.3	C,H,N	79
27	H	7-OMe	$C_{15}H_{22}N_2O$	-	138–142/0.3	C,H,N	60
28	H	5,6-$(OMe)_2$	$C_{16}H_{24}N_2O_2$	-	147–154/0.2	C,H,N	75
29	H	5-Me	$C_{15}H_{22}N_2$	-	118–125/0.3	C,H,N	84
30	H	5-SMe	$C_{15}H_{22}N_2S$	-	*c*	ND[f]	58
31	H	5-Cl	$C_{14}H_{19}ClN_2$	-	140–143/0.2	C,H,N	76
32	H	5-F	$C_{14}H_{19}FN_2$	-	118–122/0.3	C,H,N	63
33[d]	3-Me	H	$C_{15}H_{22}N_2$	-	*e*	ND	93
34[d]	4-Me	H	$C_{15}H_{22}N_2$	-	*e*	ND	95
35	3,3-Me_2	H	$C_{16}H_{24}N_2$	-	126–132/0.2	C,H,N	95
36	4,4-Me_2	H	$C_{16}H_{24}N_2$	-	115–120/0.2	C,H,N	95
37[d]	3,4-Me_2 trans	H	$C_{16}H_{24}N_2$	-	*e*	ND	98
38	3,4-Me_2 cis	H	$C_{16}H_{24}N_2$	-	*e*	ND	97

[a] Recrystallized from 95% EtOH. [b] Calcd C, 40.99; found C, 40.42. [c] Purified by flash column chromatography. [d] Diastereoisomeric mixture. [e] Used for the subsequent reaction without further purification. [f] ND = not determined.

Scheme II[a]



[a] Reagents: (a) 48% HBr, 110 °C, 4 h; (b) 3,4-$Cl_2C_6H_3CH_2COCl$, K_2CO_3, $CHCl_3$, room temperature.

acylated with 3,4-dichlorophenylacetyl chloride in dry chloroform in the presence of anhydrous potassium carbonate to give the desired racemic compounds **40–58** (Scheme II).

The pure (−) enantiomers **60** and **61** in Table V were obtained by fractional crystallization of the optically active tartaric acid salts obtained from the corresponding racemic compounds **50** and **53**. This method failed when applied to racemates **40** and **55**. To obtain the (−) enantiomers **59** and **62** the corresponding diamines **25** and **36** were resolved. Enantiomers of the diamine **25** were obtained by fractional crystallization of the optically active di-*O*-*O*′-*p*-toluoyltartaric acid salts, obtained from 1-(pyrrolidinylmethyl)-2-[(benzyloxy)carbonyl]-5-methoxy-1,2,3,4-tetrahydroisoquinoline, and subsequent removal of the *N*-(carbobenzyloxy) protecting group.

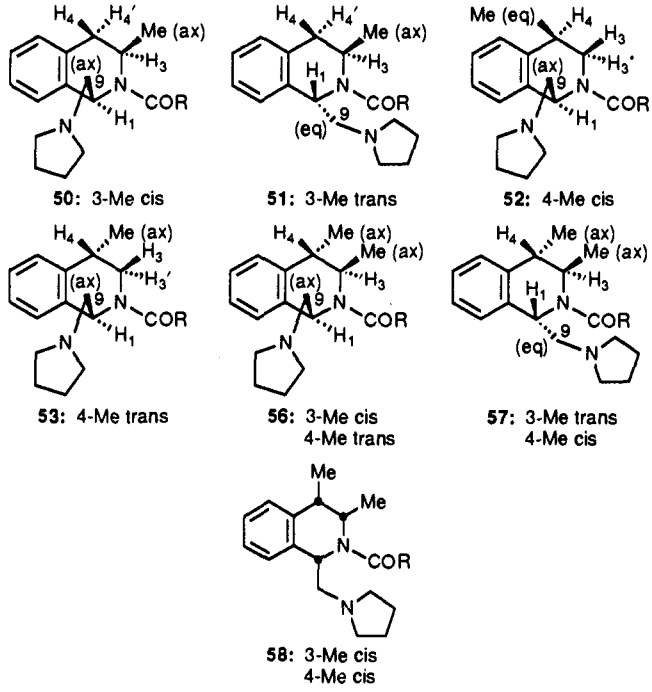
Another approach was utilized to produce the enantiomers of the diamine **36**. This racemate was treated with (*S*)-(−)-camphanic acid chloride to obtain two diastereoisomers easily separated by flash column chromatography. Subsequently, a prolonged reflux (7 days) in 48% HBr was required to give satisfactory yields and excellent optical purity of the two optically active diamines.

300-MHz ^{1}H NMR Conformational Analysis

Compounds **3b** with more than one chiral center (Table IV) were subjected to ^{1}H NMR conformational studies to investigate the relative stereochemistry and the preferred conformation of the substituents. The coupling constants $J_{H_3H_4}$ = 2.0 Hz and $J_{H_3H_4'}$ = 6.0 Hz, observed for compound **50**, indicate the pseudoaxial position of the 3-Me group. Irradiation of this group produces a NOE (ca. 9%) at one of the two protons of the pyrrolidinylmethyl group, indicating a cis relationship and the pseudoaxial conformation of this basic substituent. Very similar coupling constants, i.e. $J_{H_3H_4}$ = 2.1 Hz and $J_{H_3H_4'}$ = ca. 5 Hz, were observed for compound **51**. In this case, irradiation of the axial 3-Me substituent produces a NOE at H_1, thus demonstrating the trans relationship with the equatorial basic group. Evaluation of the coupling constants $J_{H_3H_4}$ = 12 Hz and $J_{H_3'H_4}$ = 5.7 Hz for compound **52** demonstrates the pseudoequatorial position of the 4-methyl group and the pseudoaxial position of H_3. Irradiation of this proton produces a NOE (3.2%) at one of the two protons of the pyrrolidinylmethyl group, thus indicating a cis 1,3-diaxial relationship between H_3 and this substituent. The pyrrolidinylmethyl group, therefore, is cis to the 4-methyl group.

In the diastereoisomer **53**, evaluation of the coupling constants $J_{H_3H_3'}$ = ca. 3.5 Hz and $J_{H_3'H_4}$ = ca. 3.5 Hz indicates the pseudoaxial position of the 4-methyl group. No selective irradiation on H_3,$H_{3'}$ was possible, and the relative stereochemistry was assigned as the opposite diastereoisomer of **52**. The pyrrolidinylmethyl group, trans to the 4-methyl group, must therefore be in a pseudoaxial position.

In the 3,4-*trans*-dimethyl diastereoisomers **56** and **57** the coupling constant $J_{H_3H_4}$ = ca. 2 Hz indicates that the methyl groups in both compounds are in a pseudoaxial position. Irradiation of 3-Me in **56** produces a NOE (3.0%) at the protons of the pyrrolidinylmethyl group, indicating a cis 1,3-diaxial relationship, while irradiation of the same



Me group in **57** produces a NOE (1.6%) at H_1. This latter finding is consistent with a trans relationship between the axial 3-Me and the pseudoequatorial pyrrolidinylmethyl group.

Finally, the 3,4-*cis*-dimethyl derivative **58** shows two conformers at the amide bond; the coupling constant $J_{H_3H_4}$ assumes two different values (2.0 and 6.5 Hz) thus preventing the assignment of the conformation of the two methyl groups. Irradiation of the high-field methyl group produces a NOE (ca. 3%) on the two protons of the pyrrolidinylmethyl group. This finding, together with the known cis configuration of the 3,4-dimethyl groups of the intermediates **20** and **38**, indicates that all three substituents of **58** have a cis relationship.

In conclusion, our investigation on the preferred conformation of the substituents in the series of compounds **3b** may be summarized as follows: (1) Methyl groups assume, preferentially, a pseudoaxial position (with the exception of the 4-Me cis substituent of compound **52**). (2) The same pseudoaxial conformation is assumed by the pyrrolidinylmethyl group in compounds **50**, **52**, **53**, and **56**.

Pharmacology

The antinociceptive activities of racemic compounds **40–58** 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 Tables III and IV. For comparative purposes, compound **39**[3] has also been evaluated. The binding affinities to κ, μ, and δ opioid receptors of the (−) enantiomers of some of the above compounds (**59–62**) were determined. The results obtained are shown in Table VI along with the activities of these compounds in vivo following subcutaneous administration in the MAC, MT-F, and mouse hot-plate (MHP) tests. The activities of the (−) enantiomer of the unsubstituted isoquinoline derivative **63** of the prototype κ agonist, U-50488, and the reference μ analgesic, morphine, are also reported for comparative purposes.

Results and Discussion

SAR Analysis. The effects of substitution in the isoquinoline nucleus are shown in Tables III and IV. All of the compounds therein have the pyrrolidine and the 3,4-dichlorophenylacetyl group as the basic and the acylating moiety, respectively; these features were present in the most potent compound **39** in the unsubstituted isoquinoline series.[3]

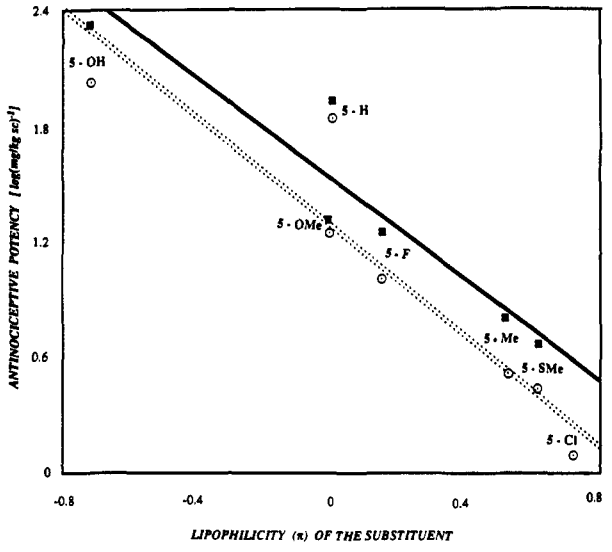


Figure 1. Graphic representation of the correlation between the antinociceptive potencies of the 5-substituted compounds expressed as log (MAC or MT-F ED_{50} sc)$^{-1}$, and the lipophilicity (π) of the substituents. The equations found are reported as follows: (■ —) log (MAC ED_{50} sc)$^{-1}$ = −1.278 (±0.25)π + 1.529 (±0.11), r = 0.927; (⊙:::) log (MT-F ED_{50} sc)$^{-1}$ = −1.443 (±0.24)π + 1.288 (±0.12), r = 0.935.

Of the four compounds obtained by introducing an hydroxy group in all positions of the benzene-condensed ring of the tetrahydroisoquinoline moiety, the 5-substituted compound[10] **40** was far more active than the 6-substituted compound **41**. Compounds with the hydroxy substituent in positions 7 and 8, **42** and **43**, respectively, were inactive. Only compound **40** was more (2-fold) potent than the reference unsubstituted isoquinoline **39**. The 5,6-dihydroxy derivative **44** was less active than the corresponding monohydroxy derivatives **40** and **41**.

The effects of introducing different substituents in position 5 of the isoquinoline nucleus are shown in Table III. In both models of antinociception, antinociceptive potency was inversely related to the lipophilicity of the substituent. A QSAR examination of the (*RS*)-5-substituted-1-(pyrrolidinylmethyl)-2-[(3,4-dichlorophenyl)acetyl]-1,2,3,4-tetrahydroisoquinolines **3a**, shown in Table III, revealed a good correlation (r = 0.927) between log (MAC ED_{50} sc)$^{-1}$ and the π values of the substituents, calculated according to Hansch et al.[11] Using a linear regression analysis, the following equation was produced:

$$\log (\text{MAC } ED_{50} \text{ sc})^{-1} = -1.278\pi + 1.529 \ (n = 6)$$

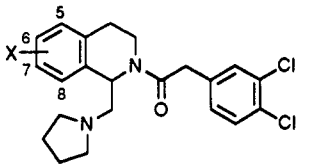
A similar correlation was found between log (MT-F ED_{50} sc)$^{-1}$ and the π values (r = 0.935, n = 7). Figure 1 is a graphic representation of the correlation between the antinociceptive potencies of the 5-substituted compounds and the lipophilicity (π) of the substituents.

The antinociceptive activities associated with the introduction of a methyl substituent in the 3 and/or 4

(10) The high antinociceptive potency of compound **40** has been recently confirmed: Hayes, A. G.; Birch, P. J.; Hayward, N. J.; Sheehan, M. J.; Rogers, H.; Tyers, M. B.; Judd, D. B.; Scopes, D. I. C.; Naylor, A. A series of novel, highly potent and selective agonists for the κ opioid receptor. *Br. J. Pharmacol.* **1990**, *101*, 944–948.

(11) Hansch, C.; Leo, A.; Unger, S. H.; Ki Kwan Kim; Nikaitani, D.; Lien, E. J. "Aromatic" substituent constants for structure–activity correlations. *J. Med. Chem.* **1973**, *16*, 1207–1216.

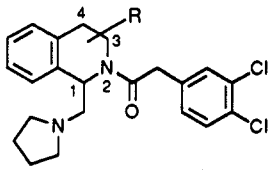
Table III. Physical Properties and Antinociceptive Activity of Racemic Compounds of General Formula 3a



compd	X	π	formula	mp, °C	anal.	recryst solvent	antinociception ED_{50},[a] μmol/kg sc MAC	MT-F
39	H	0.00	$C_{22}H_{24}Cl_2N_2O\cdot HCl$	255–257	C,H,N,Cl	EtOH	0.025 (0.017–0.042)	0.036 (0.004–0.057)
40	5-OH	–0.67	$C_{22}H_{24}Cl_2N_2O_2$	165–167	C,H,N,Cl	EtOAc	0.012 (0.010–0.014)	0.022 (0.013–0.031)
41	6-OH	–	$C_{22}H_{24}Cl_2N_2O_2$	207–208	C,H,N,Cl	EtOH	–	0.590 (0.381–0.931)
42	7-OH	–	$C_{22}H_{24}Cl_2N_2O_2$	148–150	C,H,N,Cl	EtOAc	–	>2.5
43	8-OH	–	$C_{22}H_{24}Cl_2N_2O_2$	151–153	C,H,N,Cl	EtOAc	–	>2.5
44	5,6-$(OH)_2$	–	$C_{22}H_{24}Cl_2N_2O_3\cdot HCl$	241–243	C,H,N,Cl	Me_2CO	0.985 (0.662–1.468)	1.058 (0.580–1.931)
45	5-OMe	–0.02	$C_{23}H_{26}Cl_2N_2O_2$	127–129	H,N;C,Cl[b]	*n*-hexane	0.108 (0.078–0.150)	0.125 (0.074–0.249)
46	5-Me	0.56	$C_{23}H_{26}Cl_2N_2O\cdot HCl$	220–222	C,H,N,Cl	EtOAc	0.395 (0.242–0.645)	0.827 (0.616–1.141)
47	5-SMe	0.61	$C_{23}H_{26}Cl_2N_2OS\cdot HCl$	171–174	C,H,N,S	EtOAc	0.449 (0.372–0.545)	0.795 (0.464–1.440)
48	5-Cl	0.71	$C_{22}H_{23}Cl_3N_2O\cdot HCl$	218–222	H,N,Cl;C[c]	EtOAc	>0.457	1.936 (1.212–2.947)
49	5-F	0.14	$C_{22}H_{23}Cl_2FN_2O\cdot HCl$	235–237	C,H,N,Cl,F	EtOAc	0.123 (0.088–0.173)	0.265 (0.181–0.381)

[a] In pharmacological models in vivo, n = 10 animals for each dose tested. [b] Calcd C, 63.74; Cl, 16.36; found C, 63.01; Cl, 16.94. [c] Calcd C, 55.71; found C, 54.75.

Table IV. Physical Properties and Antinociceptive Activity of Racemic Compounds of General Formula 3b

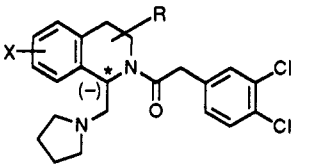


compd	R	stereochem rel to 1-subst	formula	mp, °C	anal.	recryst solvent	antinociception ED_{50},[a] μmol/kg sc MAC	MT-F
50	3-Me	cis	$C_{23}H_{26}Cl_2N_2O\cdot HCl\cdot{}^1/_3H_2O$	186–187	C,H,N,Cl	EtOAc	0.050 (0.036–0.072)	0.078 (0.051–0.125)
51	3-Me	trans	$C_{23}H_{26}Cl_2N_2O\cdot HCl\cdot {}^1/_2H_2O\cdot{}^2/_3Me_2CO$	126–130	C,H,N	Me_2CO	–	>2.5
52	4-Me	cis	$C_{23}H_{26}Cl_2N_2O\cdot HCl$	220–222	C,H,N,Cl	EtOAc	0.676 (0.486–0.942)	1.100 (0.768–1.576)
53	4-Me	trans	$C_{23}H_{26}Cl_2N_2O\cdot HCl$	214–218	C,H,N,Cl	EtOAc	0.086 (0.060–0.125)	0.110 (0.060–0.201)
54	3,3-Me_2	–	$C_{24}H_{28}Cl_2N_2O\cdot HCl$	219–221	C,H,N,Cl	Me_2CO	–	>2.5
55	4,4-Me_2	–	$C_{24}H_{28}Cl_2N_2O\cdot HCl$	270–273	C,H,N,Cl	EtOAc	0.206 (0.144–0.299)	1.639 (0.789–3.406)
56	3-Me,4-Me	3-cis,4-trans	$C_{24}H_{28}Cl_2N_2O$	117–119	C,H,N,Cl	*n*-hexane	0.025 (0.019–0.032)	0.112 (0.050–0.174)
57	3-Me,4-Me	3-trans,4-cis	$C_{24}H_{28}Cl_2N_2O$	125–129	C,H,N,Cl	MeOH	–	>2.5
58	3-Me,4-Me	3-cis,4-cis	$C_{24}H_{28}Cl_2N_2O\cdot HCl$	188–191	H,N;C,Cl[b]	EtOAc	–	>2.5

[a] In pharmacological models in vivo, n = 10 animals for each dose tested. [b] Calcd C, 61.61; Cl, 22.74; found C, 61.12; Cl, 21.89.

position of the tetrahydroisoquinoline nucleus are shown in Table IV. Among the monosubstituted compounds, the 3-Me cis (**50**) and 4-Me trans (**53**) are the most potent compounds with ED_{50} values in the MAC test of 0.050 and 0.086 μmol/kg sc, respectively. However, while the trans diastereoisomer of the 3-Me compound is almost inactive, the 4-Me cis derivative is only 10 times less potent than the corresponding trans derivative. In other words, the antinociceptive activity is more diastereoselective at the 3 than the 4 position of the isoquinoline nucleus. This could be due to the conformation of the pharmacophore (N–C–C–NCO) being affected by the close proximity of the 3-methyl substituent in the trans position; distortion of the dihedral angle between the amidic and basic nitrogens has already been shown to reduce biological activity.[2] This hypothesis is supported by the finding that, while the 4,4-*gem*-dimethyl derivative **55** maintains adequate antinociceptive potency (MAC ED_{50} = 0.206 μmol/kg sc), the corresponding 3,3-*gem*-dimethyl compound **54** is completely inactive. As expected, of the four possible diastereoisomers derived from the introduction of two methyl groups in 3 and 4 position, only compound

Table V. Physical Properties of Enantiomerically Pure Selected Compounds



compd	R	X	formula	mp, °C	anal.	recryst solvent	$[\alpha]^{20}_D$, deg (c = 1, MeOH)
59	5-OH	H	$C_{22}H_{24}Cl_2N_2O_2 \cdot HCl$	247–248	C,H,N,Cl	EtOH/Me_2CO	−13.40
60	H	3-Me cis	$C_{23}H_{26}Cl_2N_2O \cdot C_4H_6O_6$[a]	201–202	C,H,N,Cl	EtOH	−17.81
61	H	4-Me trans	$C_{23}H_{26}Cl_2N_2O \cdot C_4H_6O_6$[a]	185–187	H,N,Cl;C[b]	Me_2CO	−23.76
62	H	4,4-Me_2	$C_{24}H_{28}Cl_2N_2O \cdot HCl$	248–249	C,H,N,Cl	EtOAc	−13.95

[a] D(−)-tartrate. [b] Calcd C, 57.14; found C, 57.69.

Table VI. Pharmacological Profile of Enantiomerically Pure Selected Compounds

compd	antinociception ED_{50},[a] μmol/kg sc			receptor binding affinity K_i, nM[b]			κ/μ selectivity ratio
	MAC	MT-F	MHP	κ	μ	δ	
59	0.005 (0.004–0.006)	0.015 (0.010–0.034)	>0.13	0.09 ± 0.01	0.49 ± 0.03	7.09 (2)	5.4
60	0.024 (0.019–0.031)	0.051 (0.035–0.085)	-	0.43 ± 0.06	11.1 ± 4.36	43.6 (1)	26
61	0.031 (0.022–0.046)	0.060 (0.035–0.119)	-	0.60 ± 0.09	56.5 ± 9.5	158 ± 5.4	94
62	0.102 (0.072–0.146)	0.755 (0.496–1.206)	>7.5	2.30 ± 0.15	239 ± 9.4	1010 ± 132	104
63[c]	0.017 (0.012–0.025)	0.020 (0.012–0.029)	>0.2	0.20 ± 0.02	30.2 ± 6.4	113 ± 5	151
U-50488	1.162 (0.690–1.952)	5.781 (4.103–8.435)	>51.2	2.20 ± 0.1	616 ± 50	>10000 (2)	280
morphine	1.339 (0.984–1.819)	9.805 (5.894–12.851)	14.4	301 ± 29.8	3.30 ± 0.30	456 ± 57	0.01

[a] In pharmacological models in vivo, n = 10 animals for each dose tested. [b] Each value represents the mean from the concentration–response curves performed in triplicate, n = 3 experiments unless otherwise indicated ( ). [c] Unsubstituted compound [(−) enantiomer of **39**].

56, with the same 3-cis, 4-trans geometry as **50** and **53**, was of comparable potency. Interestingly, in all the active compounds of this series subjected to ^{1}H NMR conformational analysis (**50**,**52**,**53**,**56**) the pyrrolidinylmethyl substituent assumes a pseudoaxial conformation. A similar conformation of the basic substituent was noted with the active members of the unsubstituted isoquinoline series in solution and solid state.[3]

It is well established that κ opioid receptor binding affinity and antinociceptive activity of selective κ ligands from different chemical classes, including compounds of series **1** and **2**, reside predominantly in one enantiomer.[12-14] To determine if this was the case with the novel class of compounds described herein, selected compounds of interest, **40**, **50**, **53**, and **55** were resolved into their (+) and (−) enantiomers. Antinociceptive activity, as assessed by either the mouse abdominal constriction or mouse tail-flick tests, was found to reside only in the (−) enantiomers **59–62** (see Table VI). The (+) enantiomers were without antinociceptive activity in these models and without significant binding affinity to κ, μ, or δ opioid receptors (data not shown). On the other hand, the (−) enantiomers were very high affinity κ ligands (K_i values 0.09–2.3 nM), with varying degrees of affinity for both μ and δ receptors. All four compounds showed some selectivity for the κ rather than μ (and δ) opioid receptors. However, in this regard they were somewhat less selective than the unsubstituted isoquinoline **63**. The least selective compound is the 5-hydroxy derivative **59**, which has a K_i μ/K_i κ ratio of about 5 compared to 150 for **63**.

Compounds of the present series showed a reduced κ/μ selectivity compared to those of the piperidine series **1**, which lack the aromatic condensed ring. Thus, while the greatest ratio observed with the tetrahydroisoquinolines was ca. 100, a ratio of ca. 5000 was seen with BRL 52537A for the piperidine series.[3] The increased μ affinity of the present series of substituted isoquinolines and, in particular, of the 5-hydroxy compound **59** may be ascribed to the presence of a phenolic ring, mimicking the tyramine moiety, as in the alkaloid μ agonists of the morphinan series.

The presence of the strong interaction with μ receptors prompted us to investigate the correlation, if any, between antinociceptive activity and κ and/or μ binding affinity. Considering compounds **59–62** (Table VI), and the seven related unsubstituted (−) enantiomers described in a preceding paper,[3] using a multiple linear regression analysis for both κ and μ affinity, a lack of significance was found for the correlation between antinociceptive activity and μ affinity. Conversely, the high level of significance observed for κ affinity enabled us to produce the following equations (n = 11):

$$\text{MAC } ED_{50} \text{ sc} = 0.021\ (\pm 0.002) K_i(\kappa),\ r = 0.968$$

$$\text{MT-F } ED_{50} \text{ sc} = 0.124\ (\pm 0.011) K_i(\kappa),\ r = 0.964$$

(12) Rothman, R. B.; France, C. P.; Bykov, V.; De Costa, B. R.; Jacobson, A. E.; Woods, J. H.; Rice, K. C. Pharmacological activities of optically pure enantiomers of the κ opioid agonist, U50, 488, and its cis diastereoisomer: evidence for three κ receptor subtypes. *Eur. J. Pharmacol.* **1989**, *167*, 345–353.

(13) Meecham, K. G.; Boyle, S. J.; Hunter, J. C.; Hughes, J. An in vitro profile of activity for the (+) and (−) enantiomers of spiradoline and PD 117302. *Eur. J. Pharmacol.* **1989**, *173*, 151–157.

(14) Colle, R.; Clarke, G. D.; Dondio, G.; Giardina, G.; Petrone, G.; Sbacchi, M.; Vecchietti, V. Enantiospecificity of κ receptors: comparison of racemic compounds and active enantiomers in two novel series of κ agonist analgesics. *Chirality* **1992**, *4*, 8–15.

The good correlation found clearly demonstrates that antinociceptive activity of this series of compounds is only related to the κ binding affinity.

The functional inactivity of the μ component of the present compounds in the tail-flick test would seem to be confirmed when hot-plate and abdominal constriction data are compared. Thus, even for compound **59** (μ affinity of 0.49 nM), no antinociceptive activity was observed in the hot-plate test even at a dose almost 30-fold greater than the median effective dose in the abdominal constriction model. On the other hand, the prototype μ analgesic, morphine (μ affinity of 3.3 nM), was only 10-fold less potent in the hot-plate test than in the abdominal constriction model. While the latter model can detect the antinociceptive activity of both μ and κ agonists, only μ analgesics are effective in the hot-plate test at doses devoid of overt behavioral effects.[15] Moreover, compounds **59–63** gave no signs of physical dependence liability in the naloxone-induced jumping test in mice. In this test morphine is active.

Other nonselective opiates, such as the benzomorphan xorphanol,[16,17] which shows high binding affinity for κ, μ, and δ receptors (K_i = 0.223, 0.388, 2.26 nM, respectively) produced, in the mouse hot-plate test, a moderate protection (20–30%) at a dose approximately 2-fold greater than the median effective dose in the mouse tail-flick test. The ability of xorphanol to activate μ receptors was also shown by the dependence liability seen with this compound in the naloxone-jumping test.[18]

To investigate the possibility that the compounds were acting as partial agonists or even antagonists at the μ site, we examined whether compound **40** was able to antagonize the antinociceptive activity of morphine in the hot-plate model. At a dose active in other antinociceptive tests (0.022 μmol/kg sc) compound **40** had no effect on the antinociceptive activity of a fixed dose (14.4 μmol/kg sc) of morphine. This suggests that in vivo compound **40** is not acting as a μ opioid receptor antagonist/partial agonist. Taken together, these results indicate that although the present series of substituted tetrahydroisoquinolines are ligands at the κ, μ, and δ receptors, only the κ component is evident in functional tests in vivo. Clearly, this is not the case with some other nonselective opioid agonists such as xorphanol.

Conclusions

The effects of the introduction of substituents in the structure of the tetrahydroisoquinolines **2** may be summarized as follows: (i) The introduction of a 5-hydroxy substituent in the condensed benzene ring of the previously reported tetrahydroisoquinoline **39**[3] generated a compound (**40**) which is approximately 2-fold more potent as an antinociceptive agent than the original lead. (ii) Antinociceptive activity progressively decreases as the lipophilicity of the substituent in position 5 increases. (iii) The presence of a *trans*-methyl substituent or a *gem*-dimethyl group in position 3 negatively influences antinociceptive activity. (iv) The axial conformation of the basic substituent seems to be a common feature for the active members of the present series **3b** and the unsubstituted isoquinolines **2**.

The novel substituted compounds described herein are less selective for the κ receptor than the unsubstituted isoquinolines **2**[3] and far less selective than the piperidines **1**.[2] However, a good correlation was found between in vivo activity and κ, but not μ, receptor binding affinity. The pharmacological results for these substituted isoquinolines indicate that only the κ component is evident in functional tests in vivo.

Experimental Section

Biological Assays. κ, μ, and δ receptor binding assays were performed as previously described.[3]

In Vivo Antinociceptive Studies. Male CD-1 mice (Charles River) 20–35 g were used throughout these studies. The mouse phenyl-*p*-benzoquinone-induced abdominal constriction test (MAC) and the mouse tail-flick test (MT-F) of antinociception were performed according to the procedure described by E. Siegmund et al.[19] and F. E. D'Amour and D. L. Smith.[20] The mouse hot-plate test was performed according to the procedure described by N. B. Eddy and D. Leimbach.[21] The reaction times of mice placed onto a hot-plate maintained at 55 ± 0.5 °C were determined before and 30 min after subcutaneous injection of test drug. Either licking of the front paw or a rapid movement of the hind limbs was taken as the nociceptive endpoint. A cut-off limit of 25 s was used in these experiments. Antinociceptive response was evaluated quantally; animals were considered to have positive response if, after treatment, their reaction time was at least 2 times greater than that observed before the treatment. ED_{50} values and their 95% confidence intervals were determined by using the probit analysis method of Finney.[22] Physical dependence liability was assessed using the mouse jumping test described by J. K. Saelens et al.[23] After 4 days treatment (b.i.d) with the test drug, mice were challenged with naloxone (100 mg/kg ip). The occurrence of a stereotyped jumping behavior during the following 10 min was used as the physical dependence liability endpoint.

Chemistry. Melting points were determined with a Buchi 512 hot stage apparatus and are uncorrected. Proton NMR spectra were either 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 or $CHCl_3$ solutions with a Perkin-Elmer 241 polarimeter at the sodium D-line. The ^1H NOE effects were determined using the monodimensional difference spectroscopic technique. Typically four to six experiments were performed with a selective irradiation (2–3 s) of different protons and then subtracted from the control spectrum (off-resonance irradiation). Catalytic hydrogenations were performed with a Parr 3911 hydrogenation apparatus. 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 torr for 16 h. Elemental analyses are indicated only by the symbols of the elements; analytical results were within 0.4% of the theoretical values.

Synthesis of Known Intermediates. Chloroacetamides **4a** and **4b** in Scheme I were obtained in quantitative yield from the corresponding aromatic substituted ethylamines by treatment with chloroacetyl chloride in a stirred two-phase mixture of CH_2Cl_2

(15) Tyers, M. B. A classification of opiate receptors that mediate antinociception in animals. *Br. J. Pharmacol.* **1980**, *69*, 503–512.
(16) Kotick, M. P.; Polazzi, J. O. 17-Cyclobutylmethyl-3-hydroxy-8β-methyl-6-methylene morphinane, and methods of treating pain with them. U.S. Patent 4,259,329 (Miles Labs, Inc., 31.3.81).
(17) Howes, J. F.; Bousquet, A. R. TR5379, a new long acting narcotic antagonist analgesic. *Fed. Proc.* **1981**, *40*, abstr. 65.
(18) Unpublished in-house results.
(19) Siegmund, E.; Cadmus, R.; Lu, G. A method for evaluating both non-narcotic and narcotic analgesics. *Proc. Soc. Exp. Biol. Med.* **1957**, *95*, 729–731.
(20) D'Amour, F. E.; Smith, D. L. A method for determining loss of pain sensation. *J. Pharmacol. Exp. Ther.* **1941**, *72*, 74–79.
(21) Eddy, N. B.; Leimbach, D. Synthetic analgesics. II. Dithienylbutenyl- and dithienylbutylamines. *J. Pharm. Exp. Ther.* **1953**, *107*, 385–393.
(22) Finney, D. J. *Probit Analysis*, 3rd ed.; Cambridge University Press: Cambridge, 1971.
(23) Saelens, J. K.; Granat, F. R.; Sawyer, W. K. The mouse jumping test-a simple screening method to estimate the physical dependence capacity of analgesics. *Arch. Int. Pharmacodyn.* **1971**, *190*, 213–218.

and 50% aqueous potassium carbonate at room temperature.[24] 2-(2,3-Dimethoxyphenyl)ethylamine [3213-29-4], 2-(2-methylphenyl) ethylamine [55755-16-3], 2-(2-fluorophenyl)ethylamine [52721-69-4], and 2-(2-methylthiophenyl)ethylamine·HCl [76384-27-5] were prepared from the corresponding aldehydes by condensation with nitromethane and subsequent reduction of the substituted nitrostyrene with LAH in dry ether. 2-(2-Methylthio)benzaldehyde was prepared starting from thiosalicyclic acid.[25] α,α-Dimethyl-β-phenethylamine was prepared starting from α,α-dimethyl-β-phenethyl alcohol.[26] β,β-Dimethyl-β-phenethylamine was prepared by condensation of β-methylallylamine with benzene in the presence of an excess of aluminum chloride.[27] (*dl*)-*Threo*- and (*dl*)-*erythro*-3-phenyl-2-butylamine were prepared with a multistep synthetic pathway starting from *trans*- and *cis*-2-butene, respectively.[28] 3,4-Dichlorophenylacetyl chloride was prepared from the corresponding acid by treatment with an excess of oxalyl chloride in dry $CHCl_3$ at room temperature. 2-(2-Methoxyphenyl)ethylamine, 2-(3-methoxyphenyl)ethylamine, 2-(4-methoxyphenyl)ethylamine, 2-(2-chlorophenyl)ethylamine, β-methylphenethylamine, 2,3-dimethoxybenzaldehyde, 2-methylbenzaldehyde, 2-fluorobenzaldehyde, thiosalicyclic acid, α,α-dimethyl-β-phenethyl alcohol, β-methylallylamine hydrochloride, *trans*- and *cis*-2-butene, 3,4-dichlorophenylacetic acid, D(−)- and L(+)-tartaric acids, di-*p*-toluoyl-D(+)- and -L(−)-tartaric acids, and (1*S*)-(−)-camphanic chloride were obtained from Aldrich Chemical Co. and were used without further purification. (*dl*)-Amphetamine sulphate was supplied by Sigma Chemical Co.

General Procedure of the Preparation of Compounds 7–20 of General Formula 5a and 5b Reported in Table I. Chloroacetamides **4a** and **4b** (0.048 mol) were added portionwise, under nitrogen atmosphere, to a stirred slurry of phosphorous pentoxide (0.200 mol) in dry xylene (200 mL) at 140 °C. The reaction mixture was refluxed and vigorously stirred for 3 h; the xylene was decanted off and the solid residue carefully treated with cold water (700 mL) in an ice bath. The resulting solution was basified with concentrated NaOH and exhaustively extracted with CH_2Cl_2. The organic solution was dried over Na_2SO_4, acidified with HCl/Et_2O, and concentrated in vacuo to dryness affording the crude activated chloromethyl derivatives as hydrochloride salts. Physical properties are reported in Table I.

General Procedure for the Preparation of the Diamines 25–38 of General Formula 6a and 6b Reported in Table II. The activated chloromethyl derivatives **7–20** (12.30 mmol) were added portionwise, under nitrogen atmosphere, to a stirred solution of pyrrolidine (50 mmol) in MeOH (40 mL) cooled in an ice bath. The reaction mixture was allowed to reach room temperature and stirred overnight. After cooling in an ice bath, sodium borohydride (25 mmol) was added portionwise to the stirred solution. After 2 h, the reaction mixture was allowed to reach room temperature and evaporated. The residue, saturated with NaOH pellets, was exhaustively extracted with Et_2O. The ethereal solution, dried over Na_2SO_4 and evaporated to dryness, afforded the crude diamines. Physical properties are reported in Table II.

General Procedure for the Preparation of the Hydroxy-Substituted Diamines 21–24 of General Formula 6c Reported in Table II. The methoxy-substituted diamines **25–28** (4.5 mmol) were heated for 2 h at 130 °C with 48% HBr (20 mL). The solution was evaporated and the residue recrystallized from 95% EtOH to afford the hydroxy-substituted diamines. Physical properties are reported in Table II.

General Method of Acylation of Hydroxy-Substituted Diamines 21–24 to Obtain Compounds 40–44 in Table III. A solution of 3,4-dichlorophenylacetyl chloride (2.1 mmol) in $CHCl_3$ (10 mL) was added dropwise to a stirred solution of the diamine dihydrobromide (1.0 mmol) in the same solvent (20 mL) in the presence of Et_3N (4.2 mmol) at 0 °C. After stirring for 3 h, the reaction mixture was evaporated to dryness and the residue treated for 1 h at 80 °C with 10% HCl (50 mL). After evaporation of the solvent, the residue was dissolved in CH_2Cl_2, washed with 5% $NaHCO_3$ solution, dried, and evaporated to yield the free bases which were purified by silica gel flash column chromatography using CH_2Cl_2–MeOH containing 0.5–0.6% of 28% NH_4OH as eluent. The analytically pure samples were obtained by recrystallization; compound **44** was treated with a solution of HCl in Et_2O to give the HCl salt as white solid. Compound **43** was obtained by the above described acylation of a regioisomeric mixture of 6- and 8-hydroxy-substituted diamines and subsequent separation by flash column chromatography.

General Method of Acylation of Diamines 25–38 to Obtain Compounds 45–49 in Table III and 50–58 in Table IV. A solution of 3,4-dichlorophenylacetyl chloride (1.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of the diamine (0.9 mmol) in the same solvent (15 mL) in the presence of anhydrous potassium carbonate (1.0 mmol) at 0 °C. After stirring for 3 h, the reaction mixture was washed with 5% $NaHCO_3$ solution, dried, and evaporated to yield the free bases which were purified by silica gel flash column chromatography using CH_2Cl_2–MeOH as eluent. Where indicated 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. Diastereoisomeric pairs **50/51**, **52/53**, and **56/57** were separated, and the relative stereochemistry was assigned on the basis of the 300-MHz ^1H NMR spectra. Spectroscopic data of compounds **50–58**, determinant for the assignment of the conformation of the substituents, are reported below. The protons are indicated with the same numbering used in the 300-MHz ^1H NMR Conformational Analysis section.

Compound 50: ($CDCl_3$) δ 11.59 (s, br, H^+), 7.10–7.50 (m, 7 H), 6.15 (dd, H_1, $J_{1,9}$ = 12.5 Hz, $J_{1,9'}$ = 3.5 Hz), 4.63 (m, H_3, $J_{3,4}$ = 2.0 Hz, $J_{3,4'}$ = 6.0 Hz, J_{3,Me_3} = 6.8 Hz), 4.42 (m, 1 H), 4.35 (d, 1 H), 4.10 (m, 1 H), 3.84 (d, 1 H), 3.71 (m, H_9), 3.17 (m, $H_{9'}$), 3.11 (m, 1 H), 2.89 (m, $H_{4'}$), 2.76 (m, 1 H), 2.66 (m, H_4), 2.31 (m, 2 H), 2.06 (m, 2 H), 1.65 (d, Me_3).

Compound 51: ($CDCl_3$) δ 11.16 (s, br, H^+), 7.08–7.46 (m, 7 H), 5.59 (m, H_1, $J_{1,9}$ = ca. 6.5 Hz, $J_{1,9'}$ = ca. 4.5 Hz), 4.75 (m, H_3, $J_{3,4}$ = 2.1 Hz, $J_{3,4'}$ = ca. 5 Hz, J_{3,Me_3} = 6.5 Hz), 4.44 (m, 1 H), 4.08 (m, 1 H), 3.80 (m, 1 H), 3.75 (m, 1 H), 3.61 (m, $H_{4'}$), 3.37 (m, H_9), 3.27 (m, $H_{9'}$), 2.85 (m, 1 H), 2.73 (dd, H_4), 2.52 (m, 1 H), 2.13 (m, 2 H), 1.91 (m, 2 H), 1.01 (d, Me_3).

Compound 52: ($CDCl_3$) δ 11.38 (s, br, H^+), 7.15–7.43 (m, 6 H), 7.00 (d, 1 H), 6.07 (dd, H_1, $J_{1,9}$ = 12.0 Hz, $J_{1,9'}$ = 3.5 Hz), 4.35 (d, 1 H), 4.24 (m, 1 H), 4.12 (m, $H_{3'}$, $J_{3',3}$ = 15.0 Hz, $J_{3',4}$ = 5.7 Hz), 4.00 (m, 1 H), 3.80 (d, 1 H), 3.73 (m, H_9), 3.32 (dd, H_3, $J_{3,4}$ = 12.0 Hz), 3.04 (m, 1 H), 2.96 (m, $H_{9'}$), 2.76 (m, 1 H + H_4, J_{4,Me_4} = 6.2 Hz), 2.28 (m, 2 H), 2.06 (m, 2 H), 1.30 (d, Me_4).

Compound 53: ($CDCl_3$) δ 11.52 (s, br, H^+), 7.12–7.44 (m, 6 H), 7.05 (d, 1 H), 6.09 (dd, H_1, $J_{1,9}$ = 12.0 Hz, $J_{1,9'}$ = 3.5 Hz), 4.50 (d, 1 H), 4.25 (m, 1 H), 4.00 (m, 1 H), 3.95 (m, $H_{3'}$, $J_{3',3}$ = 14.4 Hz, $J_{3',4}$ = ca. 3.5 Hz), 3.90 (m, H_3, $J_{3,4}$ = ca. 3.5 Hz), 3.69 (d, 1 H), 3.65 (m, H_9), 3.05 (m, 1 H + H_4, J_{4,Me_4} = 7.1 Hz), 2.89 (m, $H_{9'}$), 2.71 (m, 1 H), 2.25 (m, 2 H), 2.04 (m, 2 H), 1.31 (d, Me_4).

Compound 56: ($CDCl_3$) as free base, the compound exists in a 7:3 ratio of syn and anti conformers at the amide bond; major conformer: δ 5.63 (dd, H_1, $J_{1,9}$ = 8.5 Hz, $J_{1,9'}$ = 4.0 Hz), 4.02 (m, H_3, $J_{3,4}$ = 1.5 Hz), 2.92 (dd, H_9, $J_{9,9'}$ = 11.7 Hz), 2.57 (dd, $H_{9'}$), 1.08 (d, Me_4), 1.04 (d, Me_3); minor conformer: δ 4.99 (t, H_1, $J_{1,9}$ = 6.5 Hz, $J_{1,9'}$ = 6.5 Hz), 4.83 (m, H_3, $J_{3,4}$ = 4.0 Hz), 2.98 (m, H_9, $J_{9,9'}$ = 13.5 Hz), 2.92 (m, $H_{9'}$), 1.28 (d, Me_3), 1.18 (d, Me_4).

Compound 57: ($CDCl_3$) δ 4.96 (m, H_1, $J_{1,9}$ = 8.0 Hz, $J_{1,9'} \leq$ 2 Hz), 4.05 (m, H_3, $J_{3,4} \leq$ 2 Hz), 2.84 (m, H_9), 2.73 (m, $H_{9'}$), 1.21 (d, Me_4), 0.99 (d, Me_3).

Compound 58: ($CDCl_3$) as free base, the compound exists in a 7:3 ratio of syn and anti conformers at the amide bond; major conformer: δ 5.62 (dd, H_1, $J_{1,9}$ = 8.5 Hz; $J_{1,9'}$ = 3.5 Hz), 4.08 (m,

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H_3, $J_{3,4}$ = ca. 2 Hz), 3.00 (dd, H_9, $J_{9,9'}$ = 11.5 Hz), 2.57 (dd, $H_{9'}$), 1.25 (d, Me), 0.92 (d, Me); minor conformer: δ 5.05 (t, H_1, $J_{1,9}$ = 7.0 Hz, $J_{1,9'}$ = 5.5 Hz), 5.22 (m, H_3, $J_{3,4}$ = 6.5 Hz), 3.13 (dd, H_9, $J_{9,9'}$ = 13.5 Hz), 2.98 (m, $H_{9'}$), 1.32 (d, Me), 1.05 (d, Me).

(-)-1-(Pyrrolidin-1-ylmethyl)-2-[(3,4-dichlorophenyl)-acetyl]-5-hydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (59). (±)-1-(Pyrrolidin-1-ylmethyl)-5-methoxy-1,2,3,4-tetrahydroisoquinoline (**25**) (8.13 mmol) was dissolved in Me_2CO (25 mL) containing 50% K_2CO_3 (2 mL). Benzyl chloroformate (9.77 mmol) was added dropwise at room temperature and, after 2 h, the reaction mixture was evaporated to dryness. The residue was treated with dilute HCl and extracted with Et_2O; the aqueous solution was brought to basic pH and exhaustively extracted with Et_2O to afford (±)-1-(pyrrolidin-1-ylmethyl)-2-[(benzyloxy)carbonyl]-5-methoxy-1,2,3,4-tetrahydroisoquinoline (6.12 mmol, 75%) as an oil. This racemic compound (4.87 mmol) and D-(+)-di-*p*-toluoyltartaric acid (5.00 mmol) were dissolved in Me_2CO (80 mL). The solution was left to stand at room temperature for 18 h and then filtered to give the mono D-(+)-di-*p*-toluoyltartaric acid salt of the benzyl carbamate as white crystals (2.02 mmol, 83%): $[\alpha]^{20}_D$ = +41.0 (*c* = 1, MeOH), mp 156–157 °C. Anal. C, H, N.

The parent (-)-benzyl carbamate was obtained by placing the above salt in 1 M aqueous NaOH solution (40 mL) and extracting with EtOAc. Evaporation of the solvent afforded (-)-1-(pyrrolidin-1-ylmethyl)-2-[(benzyloxy)carbonyl]-5-methoxy-1,2,3,4-tetrahydroisoquinoline as an oil: $[\alpha]^{20}_D$ = -36.9 (*c* = 1, MeOH). This compound (1.98 mmol), dissolved in 90% AcOH, was hydrogenated in a Parr apparatus in the presence of a catalytic amount of 10% Pd/C to afford the corresponding deprotected diamine in a pure enantiomeric form. Steps a and b of Scheme II were then performed on this compound as previously described in the appropriate general procedures. Chromatographic purification afforded the title compound as free base: $[\alpha]^{20}_D$ = -23.99 (*c* = 1, MeOH). Treatment of the dissolved (EtOH/Me_2CO) free base with a solution of HCl in Et_2O gave the HCl salt as white solid. Physical properties are reported in Table V.

Procedure to Obtain the Enantiomers 60 and 61 in Table V from the Corresponding Racemic Compounds 50 and 53. Racemic **50** and **53** (10.06 mmol) as free bases and D(-)-tartaric acid (10.50 mmol) were dissolved in absolute ethanol (180 mL) and Me_2CO (120 mL), respectively. The solution was left to stand at room temperature for 2 days and then filtered to give the corresponding mono D(-)-tartaric acid salts as white crystals. Their physical properties are reported in Table V.

Compound 60 (3.37 mmol, 67%), corresponding free base: $[\alpha]^{20}_D$ = -17.70 (*c* = 1, $CHCl_3$).

Compound 61 (3.22 mmol, 64%), corresponding free base: $[\alpha]^{20}_D$ = -25.48 (*c* = 1, $CHCl_3$).

(-)-1-(Pyrrolidin-1-ylmethyl)-2-[(3,4-dichlorophenyl)-acetyl]-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (62). A solution of (1*S*)-(-)-camphanic chloride (7.32 g, 33.81 mmol) in dry $CHCl_3$ (50 mL) was added dropwise to a stirred solution of the diamine **36** (7.50 g, 30.73 mmol) in the same solvent (150 mL) in the presence of anhydrous potassium carbonate (4.83 g, 35.00 mmol) at -15 °C. After stirring for 3 h, the reaction mixture was washed with 5% $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated to afford the crude diastereoisomeric couple. Silica gel flash column chromatography, eluting with a mixture of *n*-hexane/EtOAc/28% NH_4OH, 40:10:0.15, respectively, yielded the pure separated diastereoisomers of the S-(-)-camphanic acid amides formed. Diastereoisomer A (4.3 g, 10.14 mmol, 33%, oil): $[\alpha]^{20}_D$ = +3.4 (*c* = 1, $CHCl_3$). Diastereoisomer B (4.8 g, 11.32 mmol, 37%, oil): $[\alpha]^{20}_D$ = -65.4 (*c* = 1, $CHCl_3$). A and B showed very similar IR spectra (neat): 2960, 2800, 1790, 1635, 1450, 1100 cm^{-1}. Both diastereoisomers were hydrolyzed by refluxing 7 days in a mixture of AcOH (150 mL) and 48% HBr (100 mL). The solvent was evaporated and the residue carefully treated at 0 °C with 28% NH_4OH and exhaustively extracted with Et_2O. The ethereal solution, dried over Na_2SO_4 and evaporated, afforded the crude enantiomeric diamines. Silica gel flash column chromatography in a mixture of CH_2Cl_2/MeOH/28% NH_4OH, 95:7:0.5, respectively, yielded the pure enantiomeric diamines. From diastereoisomer A, 0.69 g (2.83 mmol, 28%) was obtained: $[\alpha]^{20}_D$ = -36.6 (*c* = 1, $CHCl_3$); from diastereoisomer B, 1.45 g (5.94 mmol, 53%) was obtained: $[\alpha]^{20}_D$ = +36.8 (*c* = 1, $CHCl_3$). Acylation of the (+)-diamine with 3,4-dichlorophenylacetyl chloride, following the procedure previously described, afforded the crude **62** (as free base). This compound, dissolved in EtOAc, was treated with a solution of HCl in Et_2O to give its hydrochloride salt as white crystals. Physical properties are reported in Table V.

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Registry No. **4a** (R = H, X = 5-OMe), 34162-11-3; **4a** (R = H, X = 6-OMe), 34162-12-4; **4a** (R = H, X = 7-OMe), 17639-50-8; **4a** (R = H, X = $(OMe)_2$), 65713-30-6; **4a** (R = H, X = Me), 141463-66-3; **4a** (R = H, X = SMe), 141463-67-4; **4a** (R = H, X = Cl), 34162-14-6; **4a**, 141463-68-5; **4b** (R = 3-Me, X = H), 141463-69-6; **4b** (R = 4-Me, X = H), 141463-70-9; **4b** (R = Me_2, X = H), 30572-80-6; *trans*-**4b** (R = Me_2, X = H), 141463-71-0; *cis*-**4b** (R = Me_2, X = H), 141463-72-1; **7**, 141463-73-2; **8**, 141463-74-3; **9**, 141463-75-4; **10**, 65713-31-7; **11**, 141463-76-5; **12**, 141463-77-6; **13**, 141483-94-5; **14**, 141463-78-7; **15**, 141463-79-8; **16**, 141463-80-1; **17**, 134469-47-9; **18**, 134469-46-8; **19**, 141463-81-2; **20**, 141463-82-3; **21**, 141463-83-4; **22**, 141463-84-5; **23**, 141463-85-6;)24, 141463-86-7; **25**, 141463-87-8; **26**, 141463-88-9; **27**, 141463-89-0; **28**, 141463-90-3; **29**, 141463-91-4; **30**, 141463-92-5; **31**, 141463-93-6; **32**, 141463-94-7; **33** (isomer 1), 141463-95-8; **33** (isomer 2), 141463-96-9; **34** (isomer 1), 141463-97-0; **34** (isomer 1), 141463-97-0; **34** (isomer 2), 141463-98-1; **35**, 141463-99-2; (±)-**36**, 141464-00-8; (-)-**36**, 134469-55-9; (+)-**36**, 134469-56-0; **36** camphanic acid amide (isomer 1), 141464-01-9; **36** camphanic acid amide (isomer 2), 141552-78-5; **37** (isomer 1), 141464-02-0; **37** (isomer 2), 141464-03-1; **38**, 141464-04-2; (±)-**39**, 141464-05-3; (±)-**39** free base, 135709-87-4; (-)-**39**, 141552-79-6; **40**, 141464-06-4; **41**, 141464-07-5; **42**, 141464-08-6; **43**, 141464-09-7; **44**, 141464-10-0; **44** free base, 141464-11-1; **45**, 141464-12-2; **46**, 141464-13-3; **46** free base, 141483-80-9; **47**, 141464-14-4; **47** free base, 141464-15-5; **48**, 141464-16-6; **48** free base, 141464-17-7; **49**, 141464-18-8; **49** free base, 141464-19-9; **50**, 141464-20-2; **50** free base, 141464-21-3; **51**, 141464-22-4; **51** free base, 141464-23-5; **52**, 141464-24-6; **52** free base, 141464-25-7; **53**, 141464-26-8; **53** free base, 141464-27-9; **54**, 141464-28-0; **54** free base, 141464-29-1; **55**, 141464-30-4; **55** free base, 141464-31-5; **56**, 141464-32-6; **57**, 141464-33-7; **58**, 141464-34-8; **58** free base, 141464-34-8; **59**, 125549-22-6; **60**, 141464-37-1; **60** free base, 141464-36-0; **61**, 141483-95-6; **61** free base, 141464-38-2; **62**, 134469-42-4; **62** free base, 134469-45-7; 3,4-$Cl_2C_6H_3CH_2COCl$, 6831-55-6; pyrrolidine, 123-75-1; (±)-1-(pyrrolidin-1-ylmethyl)-2-[(benzyloxy)carbonyl]-5-methoxy-1,2,3,4-tetrahydroisoquinoline, 141464-39-3; 1-(pyrrolidin-1-ylmethyl)-2-[(benzyloxy)carbonyl]-5-methoxy-1,2,3,4-tetrahydroisoquimoline D-(+)-di-*p*-toluoyltartaric acid salt, 141464-40-6; (-)-1-(pyrrolidin-1-ylmethyl)-2-[(benzyloxy)carbonyl]-5-methoxy-1,2,3,4-tetrahydroisoquinoline, 125531-01-3; (1*S*)-(-)-camphanic chloride, 39637-74-6.

Supplementary Material Available: Output of the linear regression analyses correlating antinociceptive activity with κ or with μ or with κ and μ binding affinities (3 pages). Ordering information is given on any current masthead page.