(1S)-1-(Aminomethyl)-2-(arylacetyl)-1,2,3,4-tetrahydroisoquinoline and Heterocycle-Condensed Tetrahydropyridine Derivatives: Members of a Novel Class of Very Potent κ Opioid Analgesics

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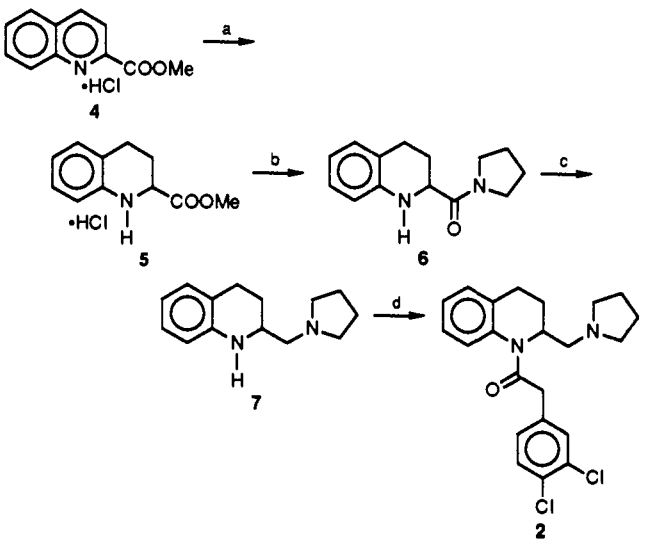
The synthesis and structure–activity relationship (SAR) of a novel class of κ opioid analgesics, 1-(aminomethyl)-2-(arylacetyl)-1,2,3,4-tetrahydroisoquinolines and (aminomethyl)-*N*-(arylacetyl)-4,5,6,7-tetrahydrothienopyridines, are described. These compounds, formally derived by the condensation of a benzene or thiophene ring on the piperidine nucleus of the recently described compounds **1**, are from 3 to 7 times more potent as antinociceptive agents and with a longer duration of action than the original lead compounds. A similar N_2–C_1–C_9–N_{10} pharmacophore torsional angle of approximately 60° was also found for this class of compounds by using X-ray and ^1H NMR analyses. The same absolute configuration (*S*) at the chiral center of the active (−) enantiomers was determined by X-ray crystallographic analysis. A varied degree of κ receptor selectivity was a feature of this novel class of antinociceptive agents (μ/κ ratio from 44 to 950 according to the nature of the basic moiety). A SAR analysis indicated that the presence of electron-withdrawing and lipophilic substituents in para and/or meta positions in the arylacetic moiety and the pyrrolidino or dimethylamino basic groups are required to optimize biological activity. The lead compounds **28**, **30**, and **48** are among the most potent antinociceptive agents (ED_{50} ca. 0.020 μM/kg sc) and κ ligands ($K_i(\kappa)$ ca. 0.20 nM) identified so far.

The existence of three main opiate receptor subtypes, μ, δ, and κ, is well established, and all three appear to be present in the central and peripheral nervous system of many species including man.[1-3] Agonists at all three receptor subtypes produce antinociception.[4] The majority of opioid drugs that are currently in clinical use as analgesic agents (e.g., morphine, fentanyl) are agonists at μ receptors.[5] It is probable that the side effects of these drugs (e.g., respiratory depression, dependence liability, and inhibition of gastrointestinal motility) also result from their μ receptor interaction.

In the expectation that κ agonists will produce clinical analgesia without the side-effect profile established by morphine-like compounds,[5] there has been considerable interest in the last decade in the development of selective κ agonists.

After the discovery of the *trans*-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide, U-50488,[6,7] a number of structurally related compounds have been identified.[8-10] In this regard, we have recently disclosed a novel class of (2*S*)-1-(arylacetyl)-2-(aminomethyl)piperidine derivatives **1** as very potent κ-selective analgesics[11] (Figure 1). The lead compounds of this novel series, **1a** (BRL 52537A) and **1b** (BRL 52656A), are the most κ/μ selective and among the most potent κ ligands identified so far. While **1b** has entered development for exploration of the therapeutic approach of κ agonists as safe analgesics, **1a** has been tritiated for use in binding

Scheme I[a]



[a] Reagents: a = H_2/PtO_2, MeOH, 15 psi; b = pyrrolidine; c = LAH, THF, 25 °C; d = 3,4-$Cl_2C_6H_3CH_2COCl$, $CHCl_3$, K_2CO_3, room temperature.

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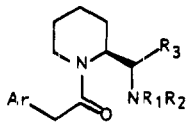
Table I. Physical Properties of Intermediates 4-26

compd	formula	mp (°C)[a] or bp (°C/mmHg) of the corresponding free base	anal.	recryst solvent[b]
4 (free base)	$C_{11}H_9NO_2$	86-87	C, H, N	*n*-hexane
5	$C_{11}H_{13}NO_2$·HCl	188-190	C, H, N, Cl	*i*-PrOH
6	$C_{14}H_{18}N_2O$	95-98	C, H, N	EtOAc
7·2HCl	$C_{14}H_{20}N_2$·2HCl	215-217	C, H, N, Cl	Me_2CO/EtOH
9	$C_{18}H_{17}NO_4$	oil	C, H, N	
10·HCl	$C_{14}H_{18}N_2O$·HCl	239-242	C, H, N, Cl	Me_2CO
11·2HCl	$C_{14}H_{20}N_2$·2HCl	255-258	C, H, N, Cl	Me_2CO
12	$C_{10}H_{12}ClNO$	66-67	C, H, N, Cl	Et_2O
13	$C_8H_{10}ClNOS$	57-59	C, H, N, Cl, S	*n*-hexane/*i*-Pr_2O
14	$C_8H_{10}ClNOS$	78-79	C, H, N, Cl, S	*i*-Pr_2O
15	$C_{12}H_{13}ClN_2O$	134-137	C, H, N, Cl	EtOAc/*i*-Pr_2O
16	$C_{12}H_{13}ClN_2O$	147-149	C, H, N, Cl	EtOAc
17	$C_{10}H_{10}ClN$·HCl	163-164	H, N, Cl; C[c]	Me_2CO
18	C_8H_8ClNS·HCl	164-166	C, H, N, Cl, S	Me_2CO
19	C_8H_8ClNS·HCl	192-193	C, H, N, Cl, S	Me_2CO
20	$C_{12}H_{11}ClN_2$·HCl	230-232	C, H, N, Cl	Me_2CO
21	$C_{12}H_{11}ClN_2$·HCl	215-218	C, H, N, Cl	Me_2CO
22a·2HCl	$C_{14}H_{20}N_2$·2HCl	115-117/0.7	C, H, N, Cl	
22b·2HCl	$C_{12}H_{18}N_2$·2HCl	91-93/0.9	C, H, N, Cl	
22c·2HCl	$C_{15}H_{22}N_2$·2HCl	128-131/0.7	C, H, N, Cl	
22d·2HCl	$C_{11}H_{16}N_2$·2HCl	100-103/0.9	C, H, N, Cl	
22e·2HCl	$C_{14}H_{20}N_2$·2HCl	100-105/0.5	C, H, N, Cl	
22f·2HCl	$C_{14}H_{22}N_2$·2HCl	106-108/0.9	C, H, N, Cl	
22g·2HCl	$C_{15}H_{22}N_2$·2HCl	120-122/0.5	C, H, N, Cl	
22h·2HCl	$C_{16}H_{26}N_2$·2HCl	118-122/0.7	C, H, N, Cl	
22i·2HCl	$C_{13}H_{18}N_2$·2HCl	108-111/0.7	C, H, N, Cl	
22j·2HCl	$C_{16}H_{24}N_2$·2HCl	127-128/0.3	C, H, N, Cl	
22k·2HCl	$C_{17}H_{26}N_2$·2HCl	140-145/0.5	H, N, Cl; C[d]	
23·2HCl	$C_{12}H_{18}N_2S$·2HCl	118-121/0.5	C, H, N, Cl, S	
24·2HCl	$C_{12}H_{18}N_2S$·2HCl	123-126/0.5	C, H, N, Cl, S	
25·2HCl	$C_{16}H_{21}N_3$·2HCl	oil	C, H, N, Cl	
26·2HCl	$C_{16}H_{21}N_3$·2HCl	oil	C, H, N, Cl	

[a] mp of compounds **22-26** were found to be >200 °C dec. [b] Recrystallization solvent of compounds **22-26** was a mixture of Me_2CO/EtOH. [c] Calcd: C, 55.57. Found: C, 55.09. [d] Calcd: C, 61.62. Found: C, 61.18. Compound **8** was supplied by Aldrich Chemical Co.



1

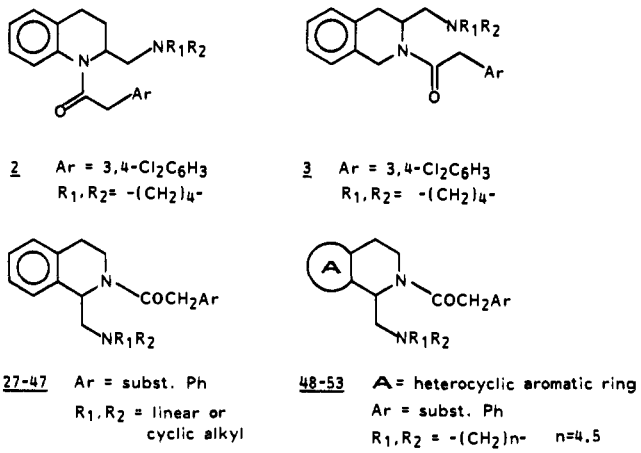
1a Ar = 3,4-$Cl_2C_6H_3$; R_1,R_2 = -$(CH_2)_4$-; R_3 = H

BRL 52537A

1b Ar = 4-$CF_3C_6H_4$; R_1,R_2 = -$(CH_2)_4$-; R_3 = H

BRL 52656A

Figure 1.



2 Ar = 3,4-$Cl_2C_6H_3$; R_1,R_2 = -$(CH_2)_4$-

3 Ar = 3,4-$Cl_2C_6H_3$; R_1,R_2 = -$(CH_2)_4$-

27-47 Ar = subst. Ph; R_1,R_2 = linear or cyclic alkyl

48-53 A = heterocyclic aromatic ring; Ar = subst. Ph; R_1,R_2 = -$(CH_2)_n$- n=4,5

Figure 2.

studies as a novel, selective, labeled κ ligand.[12]

With the aim of investigating further this novel class of compounds, we have introduced a condensed aromatic ring on the original piperidine moiety, following the suggestion that aromatic groups in nonpeptidic opiates mimic Tyr1 and/or Phe4 of the N-terminal residue of opioid peptides.[13,14]

Accordingly, we have synthesized the compounds derived from the possible condensations of the piperidine moiety of compounds **1** with a benzene ring. Among the three chemical classes obtained (compounds **2**, **3**, and **27-47**, Figure 2), only the 1-(aminomethyl)-2-(arylacetyl)-1,2,3,4-tetrahydroisoquinolines (**27-47**)[15] were more potent than the original piperidines. The replacement of the benzene ring with other aromatic heterocycles generates the novel class of (aminomethyl)-*N*-(arylacetyl)heterocycle condensed piperidine derivatives **48-53** (Figure 2),[16] which constitute an additional part of the work herein.

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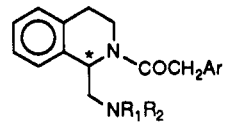
Table II. Physical Properties of Compounds 2 and 3

compd	formula	stereo	mp (°C)	anal.	recryst solvent
2	$C_{22}H_{24}Cl_2N_2O \cdot C_4H_4O_4$[a]	*RS*	159–161	C, H, N, Cl	EtOAc
3	$C_{22}H_{24}Cl_2N_2O \cdot HCl$	*RS*	228–230	C, H, N, Cl	EtOAc

[a] Maleate.

Table III. Physical Properties of Compounds 27–47



compd	formula	stereo (*)	Ar	R_1	R_2	mp (°C)	anal.	recryst solvent	$[\alpha]^{20}_D$ deg (c = 1, MeOH)
27	$C_{22}H_{24}Cl_2N_2O \cdot HCl$	(±)	3,4-$Cl_2C_6H_3$		$-(CH_2)_4-$	255–257	C, H, N, Cl	abs EtOH	
28	$C_{22}H_{24}Cl_2N_2O \cdot C_4H_6O_6$[a]	(-)	3,4-$Cl_2C_6H_3$		$-(CH_2)_4-$	185–187	C, H, N, Cl	Me_2CO	-54.3
29	$C_{23}H_{25}F_3N_2O \cdot HCl$	(±)	4-$CF_3C_6H_4$		$-(CH_2)_4-$	278–280	C, H, N, Cl	Me_2CO	
30	$C_{23}H_{25}F_3N_2O$	*S*-(-)	4-$CF_3C_6H_4$		$-(CH_2)_4-$	100–102	C, H, N, F	i-Pr_2O	-66.2[b]
31	$C_{23}H_{25}F_3N_2O$	*R*-(+)	4-$CF_3C_6H_4$		$-(CH_2)_4-$	101–103	C, H, N, F	i-Pr_2O	+66.1[b]
32	$C_{20}H_{22}Cl_2N_2O \cdot HCl$	(±)	3,4-$Cl_2C_6H_3$	Me	Me	280–281	H, N; C, Cl[c]	EtOH/MeOH	
33	$C_{20}H_{22}Cl_2N_2O \cdot C_4H_6O_6 \cdot EtOH \cdot 0.5H_2O$	(-)	3,4-$Cl_2C_6H_3$	Me	Me	157–159	C, H, N, Cl	abs EtOH	-49.7
34	$C_{24}H_{27}F_3N_2O \cdot C_4H_6O_6 \cdot 0.5H_2O$[d]	(-)	4-$CF_3C_6H_4$		$-(CH_2)_5-$	110–116	C, H, N	EtOAc	-30.5
35	$C_{22}H_{25}BrN_2O \cdot HCl$	(±)	4-BrC_6H_4		$-(CH_2)_4-$	285–287	C, H, N, Cl, Br	abs EtOH	
36	$C_{22}H_{25}N_3O_3 \cdot HCl \cdot 0.5H_2O$	(±)	4-$NO_2C_6H_4$		$-(CH_2)_4-$	149–151	C, H, N, Cl	Me_2CO	
37	$C_{22}H_{25}N_3O_3 \cdot HCl \cdot H_2O$	(±)	3-$NO_2C_6H_4$		$-(CH_2)_4-$	118–121	H, N, Cl; C[e]	Me_2CO	
38	$C_{22}H_{25}N_3O_3 \cdot HCl \cdot 0.5H_2O$	(±)	2-$NO_2C_6H_4$		$-(CH_2)_4-$	276–279	C, H, N; Cl[f]	MeOH	
39	$C_{19}H_{20}Cl_2N_2O \cdot HCl \cdot MeOH$	(±)	3,4-$Cl_2C_6H_3$	H	Me	190–191	N; C, H, Cl[g]	MeOH	
40	$C_{22}H_{24}Cl_2N_2O \cdot HCl$	(±)	3,4-$Cl_2C_6H_3$	Me	$CH_2CH{=}CH_2$	218–220	C, H, N, Cl	EtOAc	
41	$C_{22}H_{26}Cl_2N_2O \cdot HCl$	(±)	3,4-$Cl_2C_6H_3$	Et	Et	191–193	H, N; C, Cl[h]	EtOAc	
42	$C_{23}H_{26}Cl_2N_2O \cdot HCl$	(±)	3,4-$Cl_2C_6H_3$	Me	c-$C_3H_5CH_2$	193–195	C, H, N, Cl	EtOAc	
43	$C_{24}H_{30}Cl_2N_2O \cdot HCl$	(±)	3,4-$Cl_2C_6H_3$	n-Pr	n-Pr	191–193	C, H, N, Cl	EtOAc	
44	$C_{21}H_{22}Cl_2N_2O \cdot HCl$	(±)	3,4-$Cl_2C_6H_3$		$-(CH_2)_3-$	157–158	H, N; C, Cl[i]	EtOAc	
45	$C_{23}H_{26}Cl_2N_2O$	(±)	3,4-$Cl_2C_6H_3$		$-(CH_2)_5-$	122–124	C, H, N, Cl	MeOH	
46	$C_{24}H_{28}Cl_2N_2O$	(±)	3,4-$Cl_2C_6H_3$		$-(CH_2)_6-$	102–103	C, H, N, Cl	n-hexane	
47	$C_{25}H_{30}Cl_2N_2O$	(±)	3,4-$Cl_2C_6H_3$		$-(CH_2)_7-$	86–87	C, H, N, Cl	n-hexane	

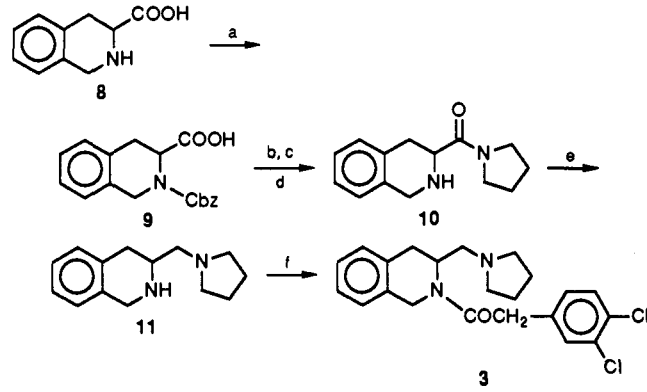
[a] D-(-)-tartrate. [b] c = 1, $CHCl_3$. [c] Calcd: C, 58.04; Cl, 25.76. Found: C, 57.34; Cl, 26.19. [d] L-(+)-tartrate. [e] Calcd: C, 60.89. Found: C, 60.34. [f] Calcd: Cl, 8.34. Found: Cl, 7.64. [g] Calcd: C, 55.63; H, 5.83; Cl, 26.63. Found: C, 54.15; H, 5.36; Cl, 24.51. [h] Calcd: C, 59.80; Cl, 24.08. Found: C, 60.42; Cl, 22.57. [i] Calcd: C, 59.23; Cl, 24.98. Found: C, 58.61; Cl, 24.46.

The present paper describes the synthesis and structure–activity relationship (SAR) of these two novel classes of very potent κ agonists. Since both antinociceptive activity and binding affinity to opiate receptors (κ, μ, and δ) are, in general, enantiospecific, the enantiomers of the compounds of particular interest were synthesized. The absolute configuration of compound **31** was determined by X-ray crystallographic analysis. Biological activity has been determined in terms of κ, μ, and δ binding affinities and in terms of antinociceptive potencies following subcutaneous and, for some compounds, oral routes of administration. For compounds of particular interest, the duration of action of the antinociceptive effect has been monitored.

Chemistry

Intermediates **4–26** (Table I) were synthesized by following methods known in the literature as described in the Experimental Section. Compounds **2** and **3** in Table II were synthesized according to Schemes I and II. Methyl quinaldate hydrochloride (compound **4**, see Scheme I) was catalytically hydrogenated over Adams catalyst in MeOH at 15 psi to afford the corresponding tetrahydro derivative **5**. Compound **6**, obtained by treating **5** with an excess of pyrrolidine, was subjected to lithium aluminum hydride reduction in THF, at room temperature, to obtain the corresponding diamine **7**. 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (compound **8**, see Scheme II) was *N*-carbobenzyloxy protected under Schotten-Baumann conditions and treated with isobutyl chloroformate and

Scheme II[a]



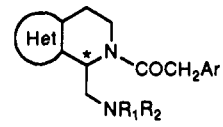
[a] Reagents: a = CbzCl, NaOH, 0 °C; b = i-BuOCOCl, Et_3N, $CHCl_3$, -15 °C; c = pyrrolidine, 0 °C; d = H_2/Pd–C, AcOH; e = LAH, THF, 25 °C; f = 3,4-$Cl_2C_6H_3CH_2COCl$, $CHCl_3$, K_2CO_3, room temperature.

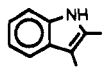
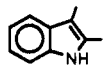
then with an excess of pyrrolidine below 0 °C. The protecting group was catalytically removed to afford compound **10**; the reduction to compound **11** was accomplished with lithium aluminum hydride.

Acylation of diamines **7** and **11** with (3,4-dichlorophenyl)acetyl chloride in dry chloroform in the presence of anhydrous potassium carbonate gave the desired racemic compounds **2** and **3**. Compounds **27–53** in Tables III and IV were synthesized according to Scheme III.

α-Chloroacetamides **12–16**, readily obtained from the

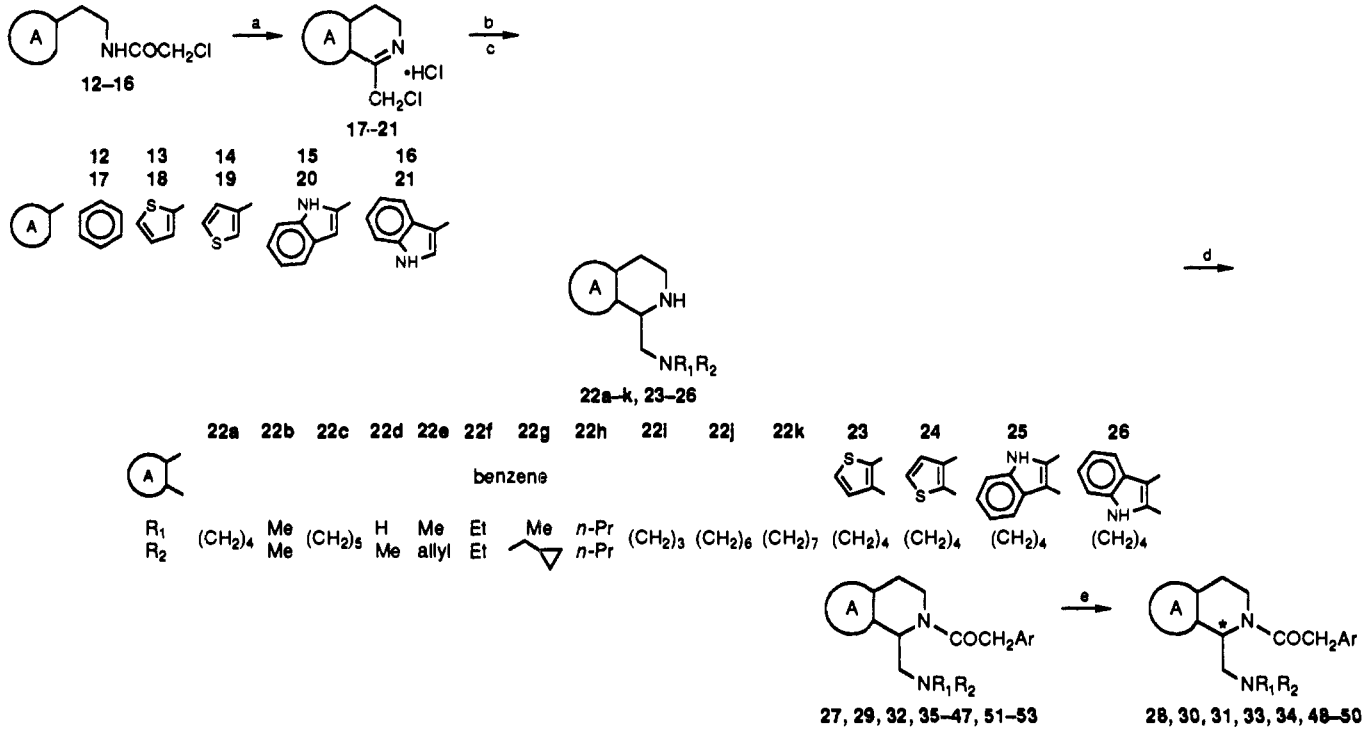
Table IV. Physical Properties of Compounds 48–53



compd	Het	formula	stereo (*)	Ar	R_1,R_2	mp (°C)	anal.	recryst solvent	$[\alpha]^{20}_D$, deg (c = 1, MeOH)
48		$C_{20}H_{22}Cl_2N_2OS\cdot HCl$	(−)	3,4-$Cl_2C_6H_3$	$-(CH_2)_4-$	209–211	C, H, N, Cl, S	Me_2CO	−73.4
49		$C_{21}H_{24}Cl_2N_2OS\cdot HCl$	(−)	3,4-$Cl_2C_6H_3$	$-(CH_2)_5-$	170–171	C, H, N, Cl, S	Me_2CO	−70.0
50		$C_{22}H_{25}F_3N_2OS\cdot H_2O\cdot C_4H_6O_6$[a]	(−)	4-$CF_3C_6H_4$	$-(CH_2)_5-$	138–142	C, H, N	EtOAc	−44.3
51		$C_{20}H_{22}Cl_2N_2OS\cdot HCl$	(±)	3,4-$Cl_2C_6H_3$	$-(CH_2)_4-$	206–208	C, H, N, Cl, S	EtOAc	
52		$C_{24}H_{26}Cl_2N_3O\cdot HCl\cdot 0.5H_2O$	(±)	3,4-$Cl_2C_6H_3$	$-(CH_2)_4-$	180–184	C, H, N	Me_2CO	
53		$C_{24}H_{26}Cl_2N_3O\cdot HCl$	(±)	3,4-$Cl_2C_6H_3$	$-(CH_2)_4-$	221–223	C, H, N, Cl	MeOH	

[a] L-(+)-tartrate.

Scheme III[a]



[a] **Reagents:** a = P_2O_5, xylene, 140 °C, 3 h or $POCl_3$, PCl_5, room temperature; b = HNR_1R_2 (excess), MeOH; c = $NaBH_4$, MeOH; d = $ArCH_2COCl$, $CHCl_3$, K_2CO_3, room temperature; e = optically active tartaric acid.

corresponding aromatic substituted ethylamines,[17] were subjected to the Bischler–Napieralski condensation using P_2O_5 as condensing agent, in refluxing xylene, to obtain 1-(chloromethyl)-3,4-dihydroisoquinoline hydrochloride[18] (**17**), or using PCl_5 in phosphorus oxychloride to obtain the heterocycle-condensed dihydropyridine hydrochlorides **18–21**.

Compounds **22–26** were obtained by treating the activated chloromethyl derivatives with an excess of the appropriate amine in dry MeOH followed by sodium borohydride reduction of the imine intermediate.[19] Acylation with suitable arylacetyl chlorides, as described above, gave the desired racemic compounds **27**, **29**, **32**, **35–47**, and **51–53**.

The pure enantiomers shown in Tables III and IV were obtained by fractioned crystallizations of the optically active tartaric acid salts obtained from the corresponding racemic compounds.

Pharmacology

The antinociceptive activities of compounds **2**, **3**, **27–53**, **1a**, and **1b** in the mouse tail-flick (MTF) and in the mouse phenyl-*p*-benzoquinone-induced abdominal constriction

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(18) Harwood, H. J.; Johnson, T. B. Isoquinoline Derivatives. *J. Am. Chem. Soc.* **1933**, *55*, 2555–2559.
(19) Griffith, R. C.; Gentile, R. J.; Robichaud, R. C.; Frankenheim, J. Cis-1,3,4,6,7,11b-Hexahydro-2-methyl-7-phenyl-2H-pyrazyno[2,1-a]isoquinoline: A New Atypical Antidepressant. *J. Med. Chem.* **1984**, *27*, 995–1003.

Table V. Antinociceptive Activity and Binding Affinity to κ, μ, and δ Opioid Receptors

compd	mouse abdomnl constrctn: ED_{50}[a] (μM/kg sc)	mouse tail-flick: ED_{50}[a] (μM/kg sc)	mouse tail-flick: ED_{50}[a] (μM/kg po)	binding affinity: k_i (nM)[b] κ	μ	δ
2		>20				
3		8.228 (5.338–14.075)				
27	0.025 (0.017–0.037)	0.036 (0.004–0.057)	0.626 (0.278–2.398)			
28	0.017 (0.012–0.025)	0.020 (0.012–0.029)	0.544 (0.336–1.131)	0.20 ± 0.02	30.2 ± 6.4	113 ± 5
29	0.027 (0.020–0.037)	0.074 (0.049–0.118)	0.467 (0.350–0.624)			
30	0.015 (0.012–0.020)	0.032 (0.014–0.049)	0.250 (0.170–0.361)	0.24 ± 0.04	10.7 ± 1.8	149 ± 11.7
31		>25		>1000 (2)	>1000 (2)	>1000 (2)
32	0.127 (0.093–0.170)	0.099 (0.049–0.148)	2.875 (1.691–5.716)			
33	0.042 (0.032–0.058)	0.075 (0.059–0.095)	2.199 (1.106–3.738)	0.51 ± 0.06	293 ± 19	746 ± 62
34	0.060 (0.041–0.091)	0.168 (0.075–0.261)	3.842 (2.106–7.007)	0.62 ± 0.02	231 ± 12.2	>1000 (2)
35		0.070 (0.008–0.111)				
36		0.038 (0.025–0.086)	0.409 (0.269–0.654)			
37		0.105 (0.058–0.192)	5.257 (3.053–19.233)			
38		>21				
39		>28				
40		0.521 (0.326–0.793)	6.875 (5.047–9.846)			
41		0.264 (0.117–0.410)	3.372 (2.486–10.139)			
42		3.388 (2.129–5.394)				
43		>23				
44		23.212 (6.054–52.193)				
45	0.101 (0.077–0.137)	0.359 (0.201–0.581)	5.160 (3.391–7.723)			
46	0.083 (0.067–0.104)	0.267 (0.167–0.406)				
47		>22				
48	0.007 (0.005–0.010)	0.018 (0.012–0.029)	0.945 (0.609–2.127)	0.22 ± 0.02	47.2 ± 12.9	153 ± 14.4
49	0.024 (0.014–0.035)	0.096 (0.025–0.217)	2.753 (1.775–6.197)	0.47 ± 0.07	445 ± 8.7	>1000
50	0.024 (0.014–0.043)	0.125 (0.077–0.261)	4.653 (2.912–7.082)	0.60 ± 0.08	420 ± 23.9	>1000
51	0.005 (0.005–0.007)	0.073 (0.041–0.119)	1.590 (0.935–3.161)	0.46 ± 0.03	47 ± 3.4	362 ± 40.0
52		>20		ca. 100 (2)	>1000 (2)	>1000 (2)
53		>20		>100 (2)	>1000 (2)	>1000 (2)
1a	0.056 (0.034–0.093)	0.135 (0.069–0.219)	2.490 (0.432–5.079)	0.31 ± 0.05	1559 ± 146	>1000 (2)
1b	0.099 (0.065–0.150)	0.373 (0.195–2.050)	3.294 (2.123–7.413)	0.64 ± 0.05	2341 ± 108	>1000 (2)
U-50488	1.162 (0.690–1.952)	5.781 (4.103–8.435)	29.060 (9.948–80.833)	2.20 ± 0.1	616 ± 50	>10000 (2)
morphine	1.339 (0.984–1.819)	9.805 (5.894–12.851)	32.581 (18.955–74.205)	301 ± 29.8	3.30 ± 0.30	456 ± 57

[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 (in parentheses).

(MAC) tests following subcutaneous administration are shown in Table V. For comparative purposes, the activities of a standard selective κ analgesic, U-50488, and the reference μ analgesic, morphine, are also reported.

For some of these compounds, including the standards, the antinociceptive potencies in the MTF test, after oral administration, and the binding affinities to the κ, μ, and δ opioid receptors in guinea pig brain are also shown.

The time course of antinociception in the MTF model has been evaluated by plotting the percentage of protection, detected after administration of equieffective doses of compounds **28**, **48**, and **1a**, against time (see Figure 3). The areas under the curve, used as a quantitative measure of the duration of action, are also reported for each of these compounds.

Results and Discussion

(1) **SAR Analysis.** Of the three possible compounds, **2**, **3**, and **27**, obtained by the condensation of a benzene ring with the piperidine nucleus of racemic **1a**, only **27** demonstrated higher antinociceptive potency than the original lead compound. Compound **27** constituted, therefore, the first member of the novel class of 1-(aminomethyl)-2-(arylacetyl)-1,2,3,4-tetrahydroisoquinolines

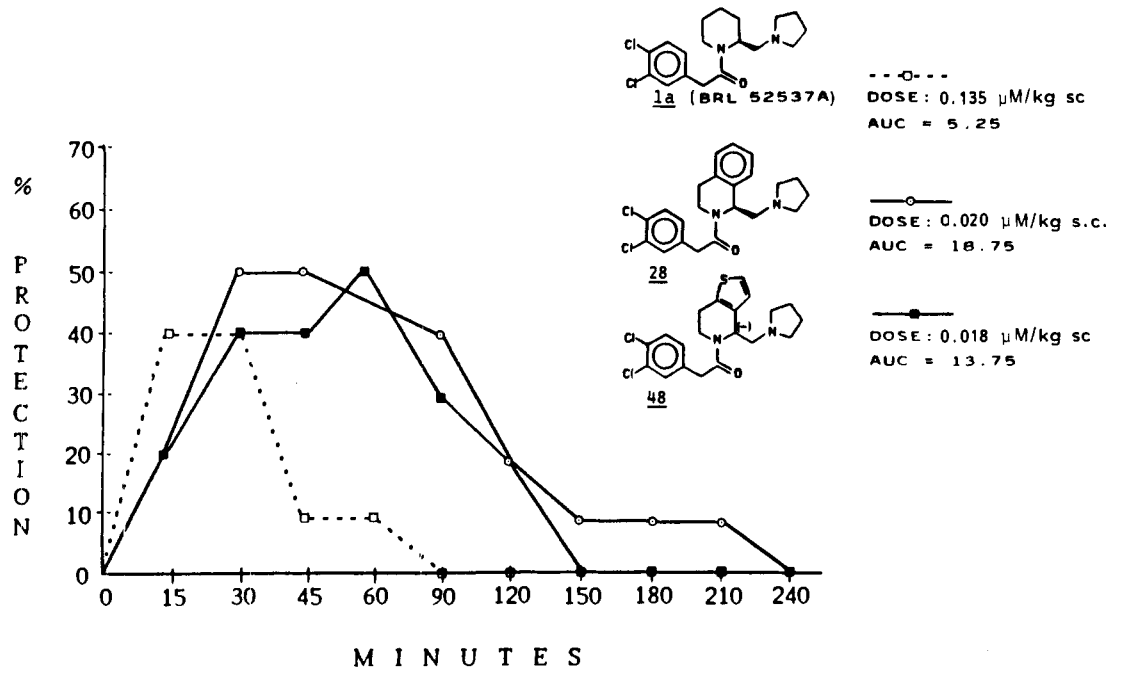

Figure 3. Time course of antinociception (mouse tail-flick model).

as highly potent antinociceptive agents.

A SAR analysis of the arylacetyl moiety led to conclusions similar to those already reported for the piperidine series 1[11b] and for the cyclohexanediamine arylacetamides series.[20] The presence of an electron-withdrawing and lipophilic substituent in para (e.g., **29**, **35**, **36**) and/or meta (e.g., **27** and **37**) positions is required for potent antinociceptive activity. Ortho substitution is not well tolerated (e.g., **38**).

Different cyclic and linear amines were introduced as basic moieties to investigate the effects of the substituents of the basic nitrogen atom. In the cyclized amine series, the highest antinociceptive activity was found with a 5-membered ring (**27**). Increasing the ring size from 6 to 8 atoms led to a reduction in antinociceptive potency.

In the linear amine series, the secondary amine (**39**) was inactive. The highest antinociceptive potency was achieved with the dimethylamino compound **32**. The activity in the MTF test progressively decreases by increasing the number of carbons of the amino group (**41** > **40** > **42** > **43**).

Two novel thienopiperidine derivatives were synthesized by following the condensation of the piperidine nucleus of compounds **1** with a heterocyclic aromatic ring. Overall, the thienopiperidine compounds showed antinociceptive potencies very similar to those of the corresponding isoquinoline derivatives (e.g., compare **48** and **28**, **50** and **34**, **51** and **27**). However, the introduction of the indole nucleus produced compounds **52** and **53**, which were completely inactive up to a dose of 20 μM/kg in the MTF test.

Since the antinociceptive activity and opiate receptor binding affinity of morphine, and of the standard κ ligands, reside mainly in one enantiomer,[21-23] compound **29**, the trifluoromethyl analogue of **27**, was therefore resolved into its (−) and (+) enantiomers (**30** and **31**) by fractional crystallization of the (−)-di-*O*,*O*′-*p*-toluoyl-L-tartrate salt. Antinociceptive activity and κ binding affinity were found to reside primarily in the (−) enantiomer **30**. The same feature was found also for the thienopiperidine series.

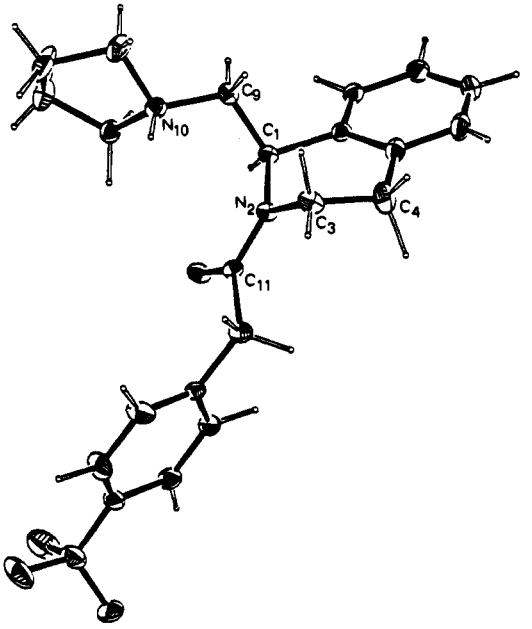

Figure 4. ORTEP drawing of the molecular structure and solid state conformation of **31**·H$^+$, with partial labeling scheme (see text). Thermal ellipsoids are drawn at 30% probability.

The X-ray crystallographic structure of the inactive (+) enantiomer, **31**, showed the absolute stereochemistry to

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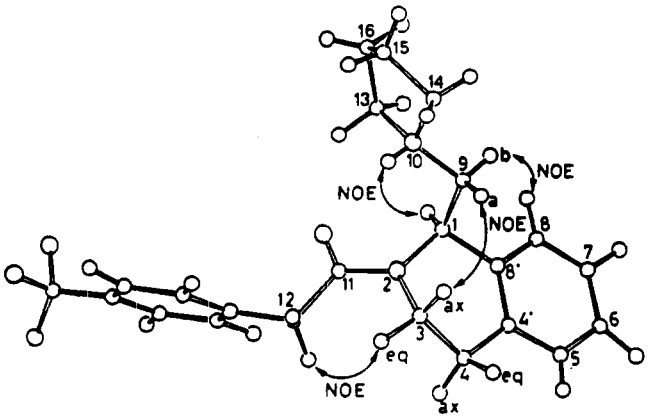

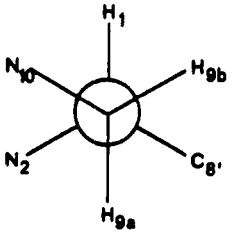

PROTONS	J (Hz) $CDCl_3$	τ X RAY
1-9a	11.7	179.5
1-9b	3.1	53.0

Figure 5. ^1H NMR conformational analysis.

be 1*R* (Figure 4), and consequently it was possible to attribute to the active (-) enantiomer **30** the 1*S* configuration. This finding is in agreement with that established for the (-) enantiomers in the piperidine series **1**.[11b]

The binding profiles of the compounds presented here are different from those exhibited by the parent piperidine series. In particular, while **1a** and **1b** demonstrated a very high selectivity for the κ receptor in relation to μ and δ sites, a varied degree of selectivity was found for the isoquinolines and thienopiperidines: μ/κ ratios from 44 (compound **30**) to 950 (compound **49**), compared to 5030 for **1a**. The nature of the basic moiety influenced κ receptor selectivity: compounds with the pyrrolidine as basic moiety are less κ selective than the corresponding piperidino and dimethylamino analogues (cf. **28**, **30**, and **48** with **33**, **34**, **49**, and **50**).

Among the isoquinolines and thienopiperidines presented in Table V, compounds **28**, **30**, and **48** are the most interesting. Thus, they are between 2 and 9 times more potent than the piperidine compound, **1a**, in both tests sc and in the MTF test following po administration.

The time course of antinociception was examined for compounds **28** and **48** in comparison with **1a**. The tetrahydroisoquinoline and the tetrahydrothienopyridine derivatives were more long acting than the related piperidine. Thus, compounds **28** and **48** were still active 120 min after subcutaneous administration, while the standard piperidine was devoid of activity (Figure 3).

(2) Conformational Studies by 300-MHz ^1H NMR and X-ray Crystallographic Analysis of the Hydrobromide of Compound 31. The coupling constants between H_3 and H_4 (Figure 5) are consistent with a pseudoaxial and pseudoequatorial position of the four protons, indicating a half chair conformation of the piperidine ring. This was confirmed by the X-ray analysis (Figure 4) of the dihedral angles formed between the above four protons and the relative carbons C_3 and C_4, indicating that C_4, $C_{4'}$, $C_{8'}$, and C_1 lie on the same plane while C_3 and N_2 stay respectively above and below that plane.

The NOE effect between H_{3ax} and H_{9a} (Figure 5) indicates that the aminomethyl substituent is in a pseudoaxial position. The high value of the coupling constant between H_1 and H_{9a} indicates that the two protons are antiperiplanar and there is a severely restricted rotation about the C_1-C_9 bond. The NOE effect between H_{9b} and H_8 indicates that N_2 and N_{10} are on the same side (see the Newman projections, Figure 5), suggesting a N_2-C_1-C_9-N_{10} dihedral angle of about 60°. This finding was confirmed by the value of 56° found in the X-ray analysis.

It is interesting to note that a pharmacophore dihedral angle of ca. 60° was found to be optimal for activity in the piperidine series.[11b] The X-ray analysis indicates that C_1-N_2-C_3-C_{11} constitutes a planar system, with angles of almost 120°, suggesting that the amidic nitrogen is trigonal. Of the two conformers generated by the planarity of the amide group, only one is present in solution and solid state: the NOE effect between H_{12} and H_{3eq} indicates that the carbonyl oxygen and the basic nitrogen are on the same side (syn conformation). The coupling constants between H_{10} and H_9 indicate that there is a restricted rotation about the C_9-C_{10} bond, confirmed also by the NOE effect between H_{10} and H_1.

Conclusions

In these novel series of compounds, the most important chemical features that determined antinociceptive activity and κ/μ receptor selectivity are as follows. (i) Condensation of a benzene or thiophene ring in C_3-C_4 of the piperidine nucleus of compounds **1** increases antinociceptive activity from 3 to 7 times. (ii) The presence of a pyrrolidine ring as basic moiety and an arylacetyl group containing electron-withdrawing and/or lipophilic substituents in the 3 and/or 4 position are essential features for optimal activity. (iii) The absolute configuration of the active (-) enantiomers was demonstrated to be 1*S* by X-ray crystallographic analysis. (iv) The same N_2-C_1-C_9-N_{10} pharmacophore dihedral angle of approximately 60°, found to be optimal for activity in the piperidine series **1**, was also found for a representative member of this novel class of compounds.

The lead compounds **28**, **30**, and **48** are more potent as antinociceptive agents and have a better duration of action than the related piperidine derivatives **1**. Although they show reduced κ/μ receptor selectivity compared to the piperidines, they are, however, still comparable with other existing compounds described as selective κ ligands such as U-50488 (see Table V) or the (±)-(5α,7α,8β)-3,4-dichloro-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4,5]-dec-8-yl]benzeneacetamide (U-62066).[8] In addition, these compounds appear among the most potent κ ligands ($K_i(\kappa)$ ca. 0.20 nM) and antinociceptive agents (MAC ED_{50} ca. 0.017 μM/kg and MTF ED_{50} ca. 0.024 μM/kg sc) described in the literature.[6,8-10,24]

The influence of the introduction of various substituents in the tetrahydroisoquinoline nucleus on biological activity is under investigation.

Experimental Section

Biological Assays. μ and δ receptor binding assays were performed as previously described.[11b]

(24) 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.

Binding to κ Sites. The highly selective κ opioid ligand, [^{3}H]-BRL 52537,[12] was used to label κ binding sites. The radioligand was incubated with brain homogenates and cold ligand for 50 min at 25 °C, filtered through Whatman GF/C filters, and washed. The radioactivity bound to the filters was counted by liquid scintillation spectrophotometry.

In Vivo Antinociceptive Studies. The mouse tail-flick test of antinociception was performed as previously described.[11b] The mouse phenyl-*p*-benzoquinone-induced (PPQ) abdominal constriction test (MAC) was performed by following the procedure of Siegmund et al.[25] The number of abdominal constriction movements induced by PPQ were monitored over an 8-min observation period and the percentage inhibition was calculated as $1 - (T/C) \times 100$, where T is mean number of abdominal constrictions in the treated group and C is mean number of abdominal constrictions in the control group.

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. The ^{1}H NOE effects were determined by using the monodimensional difference spectroscopic technique. Typically 4–6 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 on a Parr 3911 hydrogenation apparatus. Silica gel used for chromatography was kiesegel 60 (230–400 mesh) (E. Merck A.G., Darmstadt, Germany). 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. Methyl quinaldate hydrochloride (**4**) was obtained by refluxing quinaldic acid in MeOH in the presence of an excess of thionyl chloride. *N*-(Carbobenzyloxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**9**) was prepared by using Schotten–Baumann conditions. Chloroacetamides **12–16** 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 and 50% aqueous potassium carbonate at room temperature.[17] 2-(2-Thienyl)ethylamine and 2-(3-thienyl)ethylamine were obtained from the corresponding thiopheneacetonitriles by reduction with borane–methyl sulfide complex in THF at 60 °C. 2-(2-Indolyl)ethylamine was prepared according to G. A. Bhat and S. Siddappa.[26] 1-(Chloromethyl)-3,4-dihydroisoquinoline (**17**) was obtained in high yield according to H. J. Harwood.[18] Arylacetyl chlorides were prepared from the corresponding acid by treatment with an excess of oxalyl chloride in dry $CHCl_3$ at room temperature. Arylacetic acids, quinaldic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 2-phenylethylamine, 2-thiopheneacetonitrile, 3-thiopheneacetonitrile, ethyl indole-2-carboxylate, and tryptamine were obtained from Aldrich Chemical Co. and were used without further purification.

1,2,3,4-Tetrahydroquinoline-2-carboxylic Acid Methyl Ester Hydrochloride (5). Compound **4** (0.215 mol), dissolved in MeOH (180 mL), containing a solution of 20% HCl in MeOH (10 mL), was hydrogenated in a Parr apparatus in the presence of PtO_2 (2.0 g) at 15 psi for 8 h. The Pt was filtered off and the filtrate concentrated in vacuo to yield a crystalline solid. This was recrystallized from *i*-PrOH to give **5** (92%) as white needles: mp 188–190 °C; IR (KBr) 3400, 1735, 1165 cm^{-1}. Anal. ($C_{11}H_{14}ClNO_2$) C, H, N, Cl.

2-[(1-Pyrrolidinyl)carbonyl]-1,2,3,4-tetrahydroisoquinoline (6). A solution of compound **5** (22 mmol) in pyrrolidine (90 mL) and H_2O (10 mL) was stirred for 15 h at room temperature. The excess of pyrrolidine was evaporated in vacuo and the residue dissolved in CH_2Cl_2. The organic solution was washed with H_2O, dried over Na_2SO_4, and evaporated in vacuo to dryness to yield a crystalline solid. This was recrystallized from EtOAc to give **6** (71%) as a white powder: mp 95–98 °C; IR (KBr) 3420, 1630 cm^{-1}. Anal. ($C_{14}H_{18}N_2O$) C, H, N.

General Procedure for the Preparation of Diamines 7 and 11. A solution of amino amides **6** and **10** (20 mmol) in dry THF was added dropwise at room temperature to a slurry of LAH (15 mmol) in dry THF (20 mL) under a nitrogen atmosphere. After the mixture was stirred for 3 h at 25 °C, an alkaline workup afforded the crude diamines. The analytical data of **11**·2HCl are representative: yield 89%; mp 255–258 °C; IR (KBr) 3350, 2930 cm^{-1}. Anal. ($C_{14}H_{22}Cl_2N_2$) C, H, N, Cl.

3-[(1-Pyrrolidinyl)carbonyl]-1,2,3,4-tetrahydroisoquinoline (10). Isobutyl chloroformate (17.6 mmol) was added dropwise to a stirred solution of compound **9** (16.0 mmol) in dry $CHCl_3$ (100 mL) containing Et_3N (24.0 mmol), cooled below −15 °C. The reaction mixture was allowed to reach −5 °C, kept at this temperature for 15 min, and cooled again below −15 °C. Pyrrolidine (17.6 mmol) was added dropwise and the reaction mixture was allowed to reach room temperature. The organic solution was washed with H_2O, 5% $NaHCO_3$ solution, 10% citric acid solution, and a saturated NaCl solution, dried over Na_2SO_4, and evaporated in vacuo to dryness to afford the crude *N*-carbobenzyloxy carboxyamide (96%).

This intermediate, dissolved in 90% AcOH (60 mL), was hydrogenated in a Parr apparatus in the presence of 10% Pd/C (600 mg) at 40 psi for 4 h. The Pd was filtered off, and the filtrate was concentrated in vacuo and treated with 20% NaOH solution. Extraction with CH_2Cl_2 afforded compound **10** (87%), which was used without further purification in the subsequent reaction. Analytical data of **10**·HCl are reported: mp 239–242 °C; IR (KBr) 3450, 1640 cm^{-1}. Anal. ($C_{14}H_{19}ClN_2O$) C, H, N, Cl.

General Procedure for the Preparation of Compounds 18–21. Phosphorus pentachloride (86.5 mmol) was added portionwise under nitrogen atmosphere to a stirred solution of the aromatic substituted chloroacetamides **13–16** (41.4 mmol) in freshly distilled $POCl_3$ (40 mL). The temperature spontaneously reached 40 °C and, after 4 h, dry Et_2O (160 mL) was added to the stirred reaction mixture. The very hygroscopic hydrochloride salt was filtered and washed with Et_2O.

The analytical data of **19** and **20** are representative. **19**: yield 90%; mp 192–193 °C dec (recrystallized from acetone); ^{1}H NMR (CD_3OD) δ 8.42 (d, 1 H), 7.39 (d, 1 H), 5.08 (s, 2 H), 4.05 (t, 2 H), 3.30 (t, 2 H). **20**: yield 68%; mp 230–232 °C dec (recrystallized from acetone); ^{1}H NMR (CD_3OD) δ 8.50 (s br, 1 H), 7.90–7.75 (m, 1 H), 7.70–7.30 (m, 3 H), 5.15 (s, 2 H), 4.05 (t, 2 H), 3.35 (t, 2 H).

General Procedure[19] for the Preparation of the Diamines 22a–k and 23–26. The activated chloromethyl derivatives **17–21** (0.03 mol) were added portionwise to a stirred solution of the appropriate amine (0.15 mol) in MeOH (80 mL) maintained under nitrogen and 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 (0.06 mol) was added portionwise to the stirred solution. After 2 h the reaction mixture was allowed to reach room temperature and evaporated in vacuo. The residue, saturated with NaOH pellets, was exhaustively extracted with Et_2O. The ethereal solution, dried and evaporated to dryness, afforded the crude diamines.

The analytical data of **22a**, **22b**, **23**, and **25** are representative. Compound **22a**: yield 80%; bp (0.7 mmHg) 115–117 °C; IR (neat) 3340, 2970, 2800 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.15 (s, 4 H), 4.08 (dd, 1 H), 3.25–2.35 (m, 11 H), 1.90–1.65 (m, 4 H). Compound **22b**: yield 89%; bp (0.9 mmHg) 91–93 °C; IR (neat) 3330, 2950, 2820, 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.12 (s, 4 H), 4.05 (dd, 1 H), 3.25–2.42 (m, 7 H), 2.31 (s, 6 H). Compound **23**: yield 84%; bp (0.5 mmHg) 118–121 °C; IR (neat) 3320, 2960, 2800, 1440 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.95 (AB system, J = 5.27 Hz, 2 H), 4.12–3.90 (m, 1 H), 3.40–2.90 (m, 3 H), 2.88–2.35 (m, 8 H), 1.95–1.65 (m, 4 H).

Compound 25. The crude diamine was purified by silica gel column chromatography, eluting with CH_2Cl_2, containing increasing amounts of MeOH (from 2 to 8%): yield 46%; ^{1}H NMR ($CDCl_3$) δ 8.40 (s br, 1 H), 7.65–7.38 (m, 1 H), 7.36–6.90 (m, 3 H),

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4.35 (dd, 1 H), 3.65–2.30 (m, 11 H), 1.95–1.65 (m, 4 H).

General Method of Acylation of Diamines 7, 11, 22a–22k, and 23–26 To Obtain Compounds 2, 3, 27, 29, 32, 35–47, and 51–53. A solution of the aromatic acetyl 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 being stirred for 3 h, the reaction mixture was washed with 5% $NaHCO_3$ solution, dried, and evaporated in vacuo to yield the free bases, which were purified by silica gel flash column chromatography using CH_2Cl_2–MeOH as the eluent. 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 II, III, and IV).

The ^1H NMR data of compounds **3**, **29**, **51**, and **52** are representative. Compound **3** ($CDCl_3$): δ 11.70 (s br, H^+), 7.45–7.05 (m, 7 H), 5.60–5.30 (m, 1 H), 4.95 (AB system, J = 16.5 Hz, 2 H), 3.95 (AB system, J = 16.5 Hz, 2 H), 4.25–3.50 (m, 2 H), 3.45–2.50 (m, 6 H), 2.26–1.90 (m, 4 H). Compound **29** ($CDCl_3$): δ 11.80 (s br, H^+), 7.70–6.95 (m, 8 H), 6.05 (dd, 1 H), 4.50–3.35 (m, 7 H), 3.33–2.50 (m, 5 H), 2.40–1.85 (m, 4 H). Compound **51** ($CDCl_3$): δ 11.90 (s br, H^+), 7.48–7.15 (m, 4 H), 6.79 (d, 1 H), 6.21 (dd, 1 H), 4.02 (AB system, J = 16 Hz, 2 H), 4.30–3.35 (m, 5 H), 3.15–2.41 (m, 5 H), 2.20–1.98 (m, 4 H). Compound **52** ($CDCl_3$): δ 11.75 (s br, H^+), 8.42 (s br, 1 H), 7.45–6.90 (m, 7 H), 6.23 (dd, 1 H), 4.05 (AB system, J = 16.25 Hz, 2 H), 4.35–3.20 (m, 5 H), 3.10–2.30 (m, 5 H), 2.10–1.90 (m, 4 H).

General Method of Enantiomeric Separation To Obtain Compounds 28, 30, 31, 33, 34, and 48–50. The racemic compounds corresponding to the title enantiomers (11.30 mmol) and L-(+)-tartaric acid[27] (Aldrich Chemical Co., 11.80 mmol) were dissolved in the appropriate solvent (see below) and left to stand at room temperature for 18 h to 5 days. The diastereomeric salt was filtered and recrystallized from the same solvent up to a constant rotatory power. A sample of the salt was transformed into the free base by dissolving in aqueous NH_3 solution, extracting with Et_2O, and evaporating the solvent in vacuo. The mother liquors of the first crystallization were evaporated in vacuo to dryness, treated with aqueous NH_3 solution, and extracted with Et_2O to give the enriched free base, which was dissolved in the appropriate solvent. A stoichiometric amount of D-(−)-tartaric acid[28] was added to the warm solution. The diastereomeric salt crystallized on standing and was recrystallized from the same solvent up to a constant rotatory power.

A sample of the salt was transformed into the free base with the same procedure described above. Analytical data for the diastereoisomeric salts and the corresponding free bases of the enantiomers described in Tables III and IV are reported.

Compound 28: mono D-(−)-tartaric acid salt, white crystals from Me_2CO (yield 75%); $[\alpha]^{20}_D$ = −54.3° (c = 1, MeOH); mp 185–187 °C. Anal. C, H, N, Cl. Parent free base (oil): $[\alpha]^{20}_D$ = −60.3° (c = 1, $CHCl_3$).

Compound 30: mono D-(+)-di-*p*-toluoyltartaric acid salt, white crystals from EtOAc (yield 88%); $[\alpha]^{20}_D$ = +36.6° (c = 1, MeOH); mp 165–166 °C. Anal. C, H, N, F. Parent free base (**30**, slightly brown crystals): $[\alpha]^{20}_D$ = −66.2° (c = 1, $CHCl_3$); mp 100–102 °C.

Compound 31: mono L-(−)-di-*p*-toluoyltartaric acid salt, white crystals from EtOAc (yield 85%); $[\alpha]^{20}_D$ = −35.8° (c = 1, MeOH); mp 164–165 °C. Anal. C, H, N, F. Parent free base (**31**, slightly brown crystals): $[\alpha]^{20}_D$ = +66.1° (c = 1, $CHCl_3$); mp 101–103 °C.

Compound 33: mono D-(−)-tartaric acid salt·EtOH·0.5H_2O, white crystals from absolute EtOH (yield 91%); $[\alpha]^{20}_D$ = −49.7° (c = 1, MeOH); mp 157–159 °C. Anal. C, H, N, Cl. Parent free base (oil): $[\alpha]^{20}_D$ = −59.9° (c = 1, $CHCl_3$).

Compound 34: mono L-(+)-tartaric acid salt·0.5H_2O, white crystals from EtOAc (yield 80%); $[\alpha]^{20}_D$ = −30.5° (c = 1, MeOH); mp 110–116 °C. Anal. C, H, N. Parent free base (oil): $[\alpha]^{20}_D$ = −56.1° (c = 1, $CHCl_3$).

Compound 48: mono D-(−)-tartaric acid salt·0.5H_2O, white crystals from Me_2CO (yield 50%); $[\alpha]^{20}_D$ = −60.4° (c = 1, MeOH); mp 182–183 °C. Anal. C, H, N. Parent free base (oil): $[\alpha]^{20}_D$ = −81.0° (c = 1, $CHCl_3$). Hydrochloride salt as white crystals from Me_2CO: $[\alpha]^{20}_D$ = −73.4° (c = 1, MeOH); mp 209–211 °C. Anal. C, H, N, Cl, S.

Compound 49: mono L-(+)-tartaric acid salt·0.5H_2O, white crystals from Me_2CO (yield 55%); $[\alpha]^{20}_D$ = −50.0° (c = 1, MeOH); mp 170–171 °C. Anal. C, H, N. Parent free base (oil): $[\alpha]^{20}_D$ = −85.6° (c = 1, $CHCl_3$). Hydrochloride salt as white crystals from Me_2CO: $[\alpha]^{20}_D$ = −70.0° (c = 1, MeOH); mp 170–171 °C. Anal. C, H, N, Cl, S.

Compound 50: mono L-(+)-tartaric acid salt·H_2O, white crystals from EtOAc (yield 43%); $[\alpha]^{20}_D$ = −44.3° (c = 1, MeOH); mp 138–142 °C. Anal. C, H, N. Parent free base (oil): $[\alpha]^{20}_D$ = −82.1° (c = 1, $CHCl_3$).

The 300-MHz ^1H NMR of compound **31** (as hydrobromide salt) is representative. Each proton is indicated, maintaining the same numbering used in Figure 5.

Compound **31** ($CDCl_3$): δ 11.77 (s br, H_{10}), 7.53 (AB system, J = 9.5 Hz, 4 H), 7.30–7.05 (m, 4 H), 6.07 (dd, H_1, $J_{1,9a}$ = 11.7, $J_{1,9b}$ = 3.1 Hz), 4.43 (d, H_{12a}, $J_{12a,12b}$ = 16.0 Hz), 4.32 (m, H_{13a}), 4.12 (m, H_{3eq}, $J_{3eq,3ax}$ = 14.5, $J_{3eq,4eq}$ = 2.5, $J_{3eq,4ax}$ = 6.0 Hz), 4.11 (m, H_{13b}), 3.89 (d, H_{12b}), 3.81 (m, H_{3ax}, $J_{3ax,4ax}$ = 10.8, $J_{3ax,4eq}$ = 4.5 Hz), 3.73 (m, H_{9a}, $J_{9a,9b}$ = 13.2, $J_{9a,10}$ = 2.5 Hz), 3.10 (m, H_{14a}), 2.99 (m, H_{9b}, $J_{9b,10}$ = 10.0 Hz), 2.85 (m, H_{4eq}, $J_{4eq,4ax}$ = 16.5 Hz), 2.81 (m, H_{14b}), 2.75 (m, H_{4ax}), 2.40–2.00 (m, H_{15a}, H_{15b}, H_{16a}, H_{16b}).

X-ray Crystallography. X-ray crystallographic data were obtained on **31**·HBr·2H_2O, $C_{23}H_{30}BrF_3N_2O_3$, mw = 519.41. Crystals of **31**·HBr·2H_2O were grown in wet acetone by allowing the solvent to evaporate slowly at room temperature; other attempts to grow single crystals from dry acetone, dichloromethane, and chloroform failed, and only a complex intergrowth of very thin needles was obtained. The presence of water, later found in the crystal structure, seems to be necessary to obtain suitable crystals. A clear, colorless crystal, of approximate dimensions 0.25 × 0.15 × 0.12 mm, was used for the structural determination. A least-squares refinement of the setting angles of 25 intense randomly distributed reflections within 20° < θ < 28°, gave the monoclinic cell a = 6.177 (1) Å, b = 15.025 (2) Å, c = 13.289 (2) Å, β = 92.49 (1)°, V = 1232.2 (6) Å^3, Z = 2, and D_{calc} = 1.400 g cm^{-3}. A computer-controlled diffractometer (Enraf Nonius CAD4, with Mo Kα radiation, wavelength = 0.71069 Å), with an incident beam graphite monochromator, was used for data collection. A total of 4536 independent reflections were measured in the ω-scan mode to θ_{max} = 25° (±h,±k,±l octants). Corrections were applied for Lorentz and polarization effects. The periodic remeasurement of three standard reflections showed no systematic decay under the diffraction conditions. Azimuthal transmission curves (ψ scans)[29] of two reflections having χ near 90° showed no significant features, therefore no absorption correction was applied (μ(Mo Kα) = 19.96 cm^{-1}). The structure was solved by conventional Patterson and difference Fourier methods and refined by full-matrix least-squares procedures, the minimized function being $\Sigma w(|F_o| - k|F_c|)^2$. Weights were assigned as $w = 1/\sigma^2(F_o)$, where $\sigma(F_o) = \sigma(F_o^2)/2F_o$, $\sigma(F_o^2) = [\sigma^2(I) + (pI)^2]^{1/2}/LP$, and p, the ignorance factor, was set at 0.04. All non-hydrogen atoms were given anisotropic thermal parameters, while all hydrogen atoms, including those of the clathrated water molecules, were refined isotropically. The CF_3 residual has been found disordered and was interpreted as a superimposition of two models of equal population, staggered by 60° one to the other.

The handness of the crystal was determined by refining both enantiomeric models.[30] The final agreement factors for the model presented in this paper (R = 0.029, R_w = 0.035) were found to be much lower than those of its enantiomer (R = 0.067, R_w = 0.090, with poor convergence of some hydrogen atom parameters). Neutral scattering atoms were taken from ref 31; all computations have been performed by using a PDP 11/73 computer and the

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(28) D-(+)-Di-*p*-toluoyltartaric acid was used to obtain compound **30**.

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SDP crystallographic package[32] with the physical constants tabulated therein.

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Supplementary Material Available: Full list of atomic coordinates, anisotropic thermal parameters, bond distances, bond angles, and an ORTEP drawing with complete labeling scheme (14 pages). Ordering information is given on any current masthead page.

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Analogues of the 5-HT$_{1A}$ Serotonin Antagonist 1-(2-Methoxyphenyl)-4-[4-(2-phthalimido)butyl]piperazine with Reduced α_1-Adrenergic Affinity†

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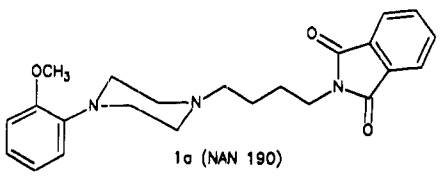
1-(2-Methoxyphenyl)-4-[4-(2-phthalimido)butyl]piperazine (NAN-190; **1a**) is a putative postsynaptic 5-HT$_{1A}$ serotonin antagonist. This high affinity ligand (K_i = 0.6 nM), although selective for 5-HT$_{1A}$ versus other 5-HT receptors, binds with nearly equal affinity at α_1-adrenergic receptors (K_i = 0.8 nM). Structure–affinity relationship studies were conducted in order to achieve an improved selectivity. Replacement of the phthalimide moiety by substituted benzamides led to retention of 5-HT$_{1A}$ affinity but to no improvement in selectivity, whereas replacement by alkyl amides proved beneficial, leading to an improvement in affinity and selectivity. Branching α to the amide carbonyl group and increased bulkiness of the alkyl moiety further improved 5-HT$_{1A}$ affinity and selectivity. 4-[4-(1-Adamantanecarboxamido)butyl]-1-(2-methoxyphenyl)piperazine (**2j**) was found to bind at 5-HT$_{1A}$ sites with high affinity (K_i = 0.4 nM) and with a 160-fold selectivity over α_1-adrenergic sites. Preliminary studies show that this agent retains antagonist activity as determined in a 5-HT$_{1A}$-coupled adenylyl cyclase assay. Further functional studies are warranted to fully characterize this agent.

Introduction

Since the discovery of the heterogeneity of serotonin (5-hydroxytryptamine, 5-HT) receptors by Gaddum and Picarelli in 1957,[1] four major populations of serotonin receptors have been identified: 5-HT$_1$, 5-HT$_2$, 5-HT$_3$, and 5-HT$_4$ (for recent reviews, see refs 2 and 3). Of these, 5-HT$_1$ receptors are heterogeneous and are comprised of at least the 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1C}$, and 5-HT$_{1D}$ subtypes.[2] The 5-HT$_{1A}$ subtype has been best characterized, owing largely to the availability of a selective and potent agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT).[4] However, research in the 5-HT$_{1A}$ area continues to be hampered by the lack of selective antagonists.

Investigations in our laboratory of the structure–affinity relationships (SAFIR) of arylpiperazines have led to the development of high-affinity ligand, 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)butyl]piperazine (NAN-190; **1a**) that was reported to be the first antagonist at 5-HT$_{1A}$ sites.[5,6] Although, **1a** is selective for 5-HT$_{1A}$ sites over other serotonergic sites, it possesses an almost equal affinity for α_1-adrenergic receptors. The action of this ligand as an antagonist, or as a partial agonist, at 5-HT$_{1A}$ receptors is still under debate. Rydelek-Fitzgerald et al.[7] have proposed that **1a** is a partial agonist at postsynaptic sites with very low intrinsic activity, while Hjorth and Sharp[8] have suggested that **1a** is an antagonist at postsynaptic sites and a partial agonist at presynaptic sites. It has also



1a (NAN 190)

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