Pergamon

Bioorganic & Medicinal Chemistry 9 (2001) 1325–1335

BIOORGANIC & MEDICINAL CHEMISTRY

A Multireceptorial Binding Reinvestigation on an Extended Class of σ Ligands: *N*-[ω-(Indan-1-yl and Tetralin-1-yl)alkyl] Derivatives of 3,3-Dimethylpiperidine Reveal High Affinities Towards σ_1 and EBP Sites

Francesco Berardi,* Savina Ferorelli, Nicola Antonio Colabufo, Marcello Leopoldo, Roberto Perrone and Vincenzo Tortorella

Dipartimento Farmaco-Chimico, Università di Bari, via Orabona 4, I-70126 Bari, Italy

Received 4 October 2000; accepted 5 January 2001

Abstract—New 1-[ω-(2,3-dihydro-1*H*-inden-1-yl)- and (2,3-dihydro-5-methoxy-1*H*-inden-1-yl)alkyl]- and 1-[ω-(1,2,3,4-tetrahydronaphthalen-1-yl)- and (6-methoxy- or 6-fluoro-1,2,3,4-tetrahydronaphthalen-1-yl)alkyl] derivatives of 3,3-dimethylpiperidine were synthesized, as homologous compounds of an existing series of σ ligands, in order to carry out σ receptor subtypes structure–affinity relationships. The new compounds and some of their related analogues, already reported, were tested in new multireceptorial radioligand binding assays. As reference compounds, the known σ_1 ligands SA 4503, BD 1008 and NE 100 were also prepared and tested. All reported compounds showed high σ_1 affinity assayed by (+)-[^{3}H]-pentazocine on guinea-pig brain (apparent $K_i = 1.75$–72.2 nM) and moderate or low σ_2 affinity by [^{3}H]-DTG on rat liver, in contrast with previous results. One tertiary amine function spaced by a five-membered chain from a phenyl group is the structural feature shared by the most active compounds **26** and **43** and some reference σ_1 ligands. The reported σ_1 ligands, including reference compounds, also demonstrated a high affinity towards EBP (Δ_8–Δ_7 sterol isomerase) site (apparent $K_i = 0.48$–14.8 nM) and some of them (**37** and **44**) were good ligands at L-type Ca^{++} channel. 1-[4-(2,3-Dihydro-1*H*-inden-1-yl)butyl]-3,3-dimethylpiperidine (**26**) was the best mixed σ_1 and EBP ligand (apparent $K_i = 1.75$ and 1.54 nM, respectively) with a good selectivity versus σ_2 receptor (138- and 157-fold, respectively).

Introduction

The design of selective σ ligands has become an attractive field in the search of new agents for schizophrenia,[1–3] depression,[4] memory impairment,[5] cocaine-induced toxicity,[6] neuronal damages[7] and other CNS-related pathologies.[8] Moreover, several human tumoral cell lines express σ receptors,[9] so that positron emission tomography (PET) cancer diagnosis is another applicative area for σ ligands.[10] On the basis of molecular size and pharmacological profile, two σ receptor subtypes are universally recognized and functionally distinguished.[11,12] σ_1 Receptors are involved in several modulations, such as those of NMDA-stimulated neurotransmitter systems,[13] synthesis and release of dopamine and acetylcholine and opiate analgesia. σ_2 Receptor regulates intracellular Ca^{++} storage and has been proved to be implicated in the cytotoxicity and cell apoptosis.[14] Several compounds, including (+)-benzomorphans[15] and more simplified structures containing substituted piperidine or piperazine, have been reported to bind at σ_1 receptor with high affinity,[16] whereas high-affinity and selective σ_2 receptor ligands are needed to better investigate σ_2 receptor nature and functions. Indeed, the design of really selective σ receptor subtype ligands is complicated by the affinity towards other receptor systems, such as dopamine D_2, serotonin 5-HT_{1A} and 5-HT_2, opiate, NMDA complex and others. Moreover, the recent cloning of human σ_1 receptor[17] has evidenced that its structure is different from other known mammalian proteins. It shares a similarity with the ERG-2p yeast isomerase but not with emopamil binding protein (EBP), the human sterol Δ_8–Δ_7 isomerase.[18] Nevertheless, several σ_1 ligands and Ca^{++} channel modulators have shown affinities for EBP site.[19] The relationship between σ receptor and EBP site is a novel intriguing area of challenge in designing new selective ligands. In a recent work, we began to investigate σ-subtype

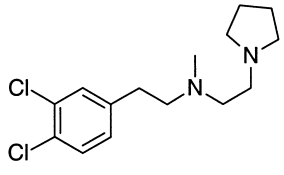
*Corresponding author. Tel.: +39-80-544-2751; fax: +39-80-544-2231; e-mail: berardi@farmchim.uniba.it

0968-0896/01/$ - see front matter
PII: S0968-0896(01)00011-6

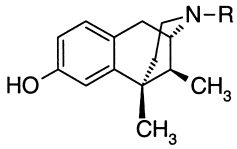
selectivity in a new class of 3,3-dimethyl-*N*-[ω-(tetralin-1-yl)-alkyl]piperidine and some related compounds.[20] Although several compounds reached very high σ_2 affinities and selectivities, no clear structure–affinity relationship emerged. As an extension of that work, more related structures were synthesized. The effects of the length of the intermediate alkyl chain between 3,3-dimethylpiperidine moiety and the tetralin or the indane nucleus appeared particularly interesting to focus upon. In fact, previously assayed ligands, bringing two- to five-methylene spacer, purportedly appeared to indifferently bind at σ_1 and σ_2 receptors with high affinity. In this paper, we reinvestigate σ_1/σ_2 selectivity of such compounds by more updated and reliable binding methods. In another contemporary work, compounds **23**, **37** and **42**–**44** demonstrated Ca^{++} antagonist activity, by inhibiting electrically-induced stimulations in guinea pig ileum longitudinal muscle/myenteric plexus preparations and they gave completely different results, when reexamined with new σ binding protocols. This finding led us to assay them for L-type Ca^{++} channel affinity. In this work, we extended that binding assay to the ligands displaying the highest σ_1 affinities to prove their selectivities. Further suggestions for a reinvestigation came from preliminary results of another collaborative work, that revealed the ability of compounds **37** and (*S*)-(+)-**39** to inhibit a post-squalenic step of cholesterol biosynthesis and cell proliferation in rat aortic myocytes.[21] In order to evidence the pharmacological similarity between σ_1 receptor and EBP,[22] we assayed a limited number of reported compounds in the EBP binding. We also prepared the known σ_1 ligands SA 4503, claimed to be an agonist, and BD 1008 and NE 100 reported to be antagonists (Chart 1) and we tested them as reference compounds in the above binding assays. They were chosen because they were also used in the above Ca^{++} antagonism assays and were easy to synthesize.

Chemistry

The synthesis of these classes of compounds has already been reported.[20] The properties of new final compounds are described in Table 1. Their spectral data and those of their new respective intermediate compounds are reported in the Experimental. No longer commercially available 3,3-dimethylpiperidine[23] was prepared in a new way, described in Scheme 1. 2,2-Dimethylglutaric acid (**1**) was derivatized to the acyl chloride with $SOCl_2$ and then with benzylamine to the monoamide, which was heated at 200 °C to give the imide **2**. Reduction to 3,3-dimethyl-1-benzylpiperidine (**3**) with $LiAlH_4$ and subsequent debenzylation by catalytic hydrogenation afforded 3,3-dimethylpiperidine (**4**). For compounds **24** and **41**, with an ethylenic intermediate chain, the synthetic pathways are reported in Scheme 2. The esters **6a** and **6b** were prepared starting from corresponding 1-indanone (**5a**) and 6-methoxy-1-tetralone (**5b**) via α,β-unsaturated esters and were reduced to the alcohols **7a,b** with $LiAlH_4$.[24] Derivatization of **7a,b** to the methylsulfonate derivatives **8a,b** with methanesulfonyl chloride and subsequent reaction with 3,3-dimethylpiperidine

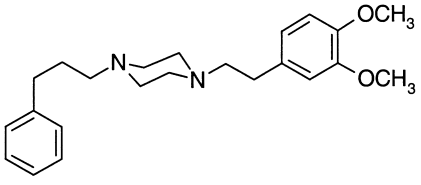


BD1008

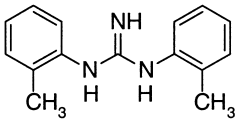


(+)-SKF 10047: R=

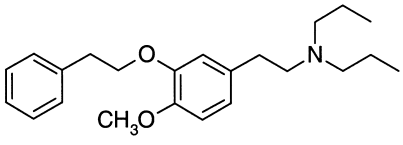
(+)-PENTAZOCINE: R=



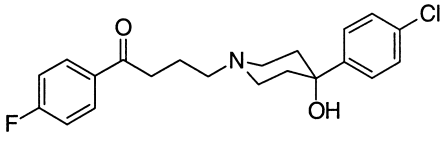
SA4503



DTG



NE100



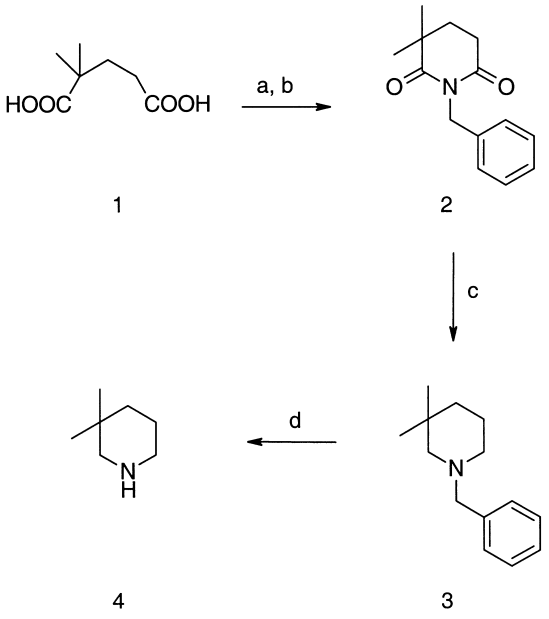
HALOPERIDOL

Chart 1.

Table 1. Physical properties of new compounds

Compound[a]	Yield (%)	Column chromatography eluent	Formula[b]	Recryst. solv.	Mp (°C)
24	84	—	$C_{18}H_{27}N\cdot HCl$	CH_3OH/Et_2O	203–205
26	45	$CHCl_3$	$C_{20}H_{31}N\cdot HCl$	CH_2Cl_2/Et_2O	158–159
27	61	CH_2Cl_2/CH_3OH, 19:1	$C_{21}H_{33}N\cdot HCl$	CH_2Cl_2/Et_2O	160
28	44	$CHCl_3$	$C_{22}H_{35}N\cdot HCl$	CH_2Cl_2/Et_2O	160–161
31	53	$CHCl_3$	$C_{21}H_{33}NO\cdot HCl$	CH_2Cl_2/Et_2O	168–169
32	57	CH_2Cl_2/CH_3OH, 19:1	$C_{22}H_{35}NO\cdot HCl$	CH_2Cl_2/Et_2O	125–127
33	50	$CHCl_3/CH_3OH$, 19:1	$C_{23}H_{37}NO\cdot HCl\cdot 1/2H_2O$	CH_2Cl_2/Et_2O	186–187
38	51	$CHCl_3$	$C_{23}H_{37}N.HCl$	CH_2Cl_2/Et_2O	138–139
41	53	CH_2Cl_2/CH_3OH, 19:1	$C_{20}H_{31}NO\cdot HCl$	CH_3OH/Et_2O	211–214
45	65	$CHCl_3$	$C_{24}H_{39}NO\cdot HCl$	CH_2Cl_2/Et_2O	123–124
48	60	$CHCl_3$	$C_{21}H_{32}FN\cdot HCl\cdot 2/3H_2O$	CH_3OH/Et_2O	148–150
49	46	$CHCl_3$	$C_{22}H_{34}FN\cdot HCl$	CH_2Cl_2/Et_2O	152–153

[a]White to ivory-colored crystalline powders; for their structures see Table 2.
[b]Analyses for C, H, N; the results were within ±0.4% of the theoretical values for the formulas given.

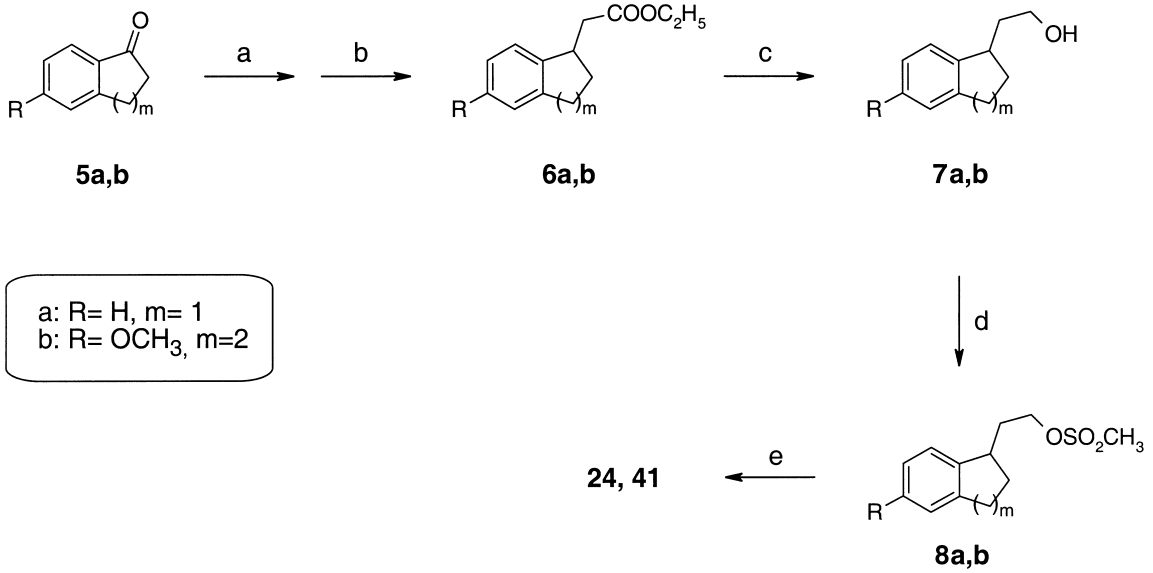


Scheme 1. Reagents: (a) $SOCl_2$; (b) benzylamine; (c) $LiAlH_4$, THF; (d) H_2, 10% Pd/C, MeOH.

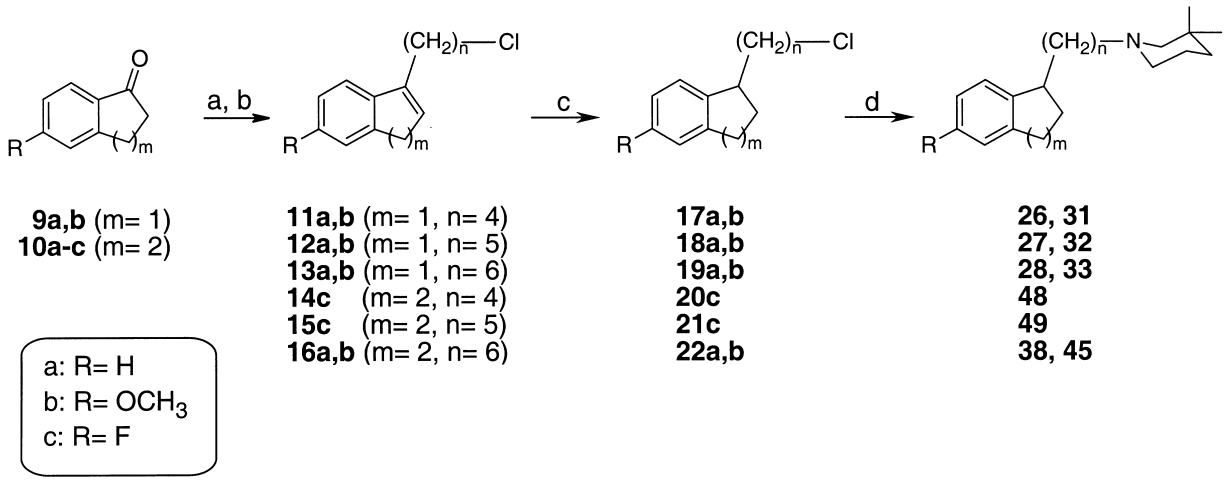
yielded compounds **24** and **41**. The remaining new compounds were prepared according to the yet reported procedure, starting from corresponding indanones **9a,b** or tetralones **10a–c** and the appropriate ω-chloro-*n*-alkylmagnesium bromide (Scheme 3).[25] The compounds **28**, **33**, **38** and **45**, with a six-membered alkyl chain, were obtained from the respective 1-indanone or 1-tetralone and 1-bromo-6-chloro-*n*-hexane. For the synthesis of fluorinated compounds **48** and **49**, the starting product 6-fluoro-1-tetralone (**10c**) was prepared following a known synthetic pathways.[26] The compounds SA 4503 [1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine],[27] BD 1008 [*N*-[2-(3,4-dichlorophenyl)ethyl]-*N*-methyl-2-(1-pyrrolidinyl)ethylamine],[28] and NE 100 [*N*,*N*-dipropyl-2-[4-methoxy-3-(2-phenylethoxyl)phenyl]-ethylamine][29] were synthesized according to the respective literature.

Pharmacology

The reported compounds were evaluated as hydrochloride salts (compound **30** as hydrogen oxalate) for in vitro affinity by radioreceptor binding assays. The specific



Scheme 2. Reagents: (a) NaH (60% mineral oil dispersion), triethyl phosphonoacetate; (b) H_2, 10% Pd/C; (c) $LiAlH_4$; (d) CH_3SO_2Cl; (e) 3,3-dimethylpiperidine.



Scheme 3. Reagents: (a) 4-chloro-*n*-butyl-MgBr ($n=4$), 5-chloro-*n*-pentyl-MgBr ($n=5$), 6-chloro-*n*-hexyl-MgBr ($n=6$); (b) HCl; (c) H_2, 10% Pd/C; (d) 3,3-dimethylpiperidine.

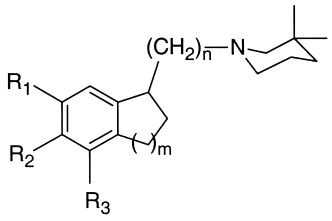
radioligands and tissue sources were respectively: (a) σ_1 receptor, (+)-[^{3}H]-pentazocine ((+)-[2*S*-2α,6α,11*R*)]-1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocine-8-ol), guinea-pig brain membranes without cerebellum; (b) σ_2 receptor, [^{3}H]-DTG (1,3-di(2-tolyl)guanidine) in the presence of 1 μM (+)-pentazocine to mask σ_1 receptors, rat liver membranes; (c) L-type Ca^{++} channel, (−)-[^{3}H]-D 888 (desmethoxyverapamil), rat brain membranes; (d) EBP sites, (±)-[^{3}H]-emopamil, guinea-pig liver membranes; (e) 5-HT_{1A} receptor, [^{3}H]-8-OH-DPAT, rat hippocampus membranes; (f) MK 801 site, [^{3}H]-MK 801 in the presence of 100 μM D-glutamate and 100 μM L-glycine to mask corresponding sites in the NMDA receptor, rat brain cortex. The following compounds were used to define specific binding, reported in parentheses: (a) haloperidol ((4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone) (75–90%), (b) DTG (75–90%), (c) (±)-verapamil (68–82%), (d) (±)-ifenprodil (65%), (e) 8-OH-DPAT (80%) and (f) MK 801 (95%). They were chosen as presently the most used reference compounds, according to the methods described in Experimental.

Concentrations required to inhibit 50% of radioligand specific binding (IC_{50}) were determined by using six to nine different concentrations of the drug studied in three experiments with samples in duplicate. The apparent inhibition constants (K_i) were determined from IC_{50} values by using the Cheng–Prusoff equation.

Results and Discussion

All tested compounds **23**–**49** (Table 2) were σ_1 ligands with high to moderate affinity (apparent $K_i = 1.75$ to 72.5 nM). For several reinvestigated tetralin derivatives, these results are rather different from those previously obtained[20] on rat brain with (+)-[^{3}H]-SKF 10047. It is presumable that differences among the species occur for the tissues used. However, the present results can be considered more reliable, because of a higher σ_1 receptor density in the guinea-pig brain and higher σ_1 affinity and selectivity of (+)-[^{3}H]-pentazocine compared to (+)-[^{3}H]-SKF 10047. For the latter we found $K_i = 58.8 \pm 5.1$ nM at the σ_1 receptor on such tissue. On the other hand, the σ_2 affinities measured on rat liver were generally lower than those on guinea-pig brain reported for the same compounds.[20] Indeed, previously reported σ_2 affinities were actually σ total affinities, as measured in the absence of any σ_1 masking agent. The present reinvestigation and widening on tetralin and indane derivatives can now allow a better definition of σ receptor subtypes structure–affinity relationship for 3,3-dimethylpiperidine derivatives. These compounds showed higher affinities towards σ_1 than σ_2 receptor, or comparable in few cases (compounds **24, 25, 27** and **34**), consistently with their structural similarity with pentazocine. The most active ligand at σ_1 receptor was compound **26** ($K_i = 1.75$ nM), which also presented the best selectivity versus σ_2 receptor (138-fold). In the remaining homologous of the indane series **24**–**28** the σ_1 affinity does not change with the length of intermediate alkyl chain. Similarly, the tetralin derivatives of the series **34**–**38** displayed comparable σ_1 affinities and selectivities versus σ_2 receptor. Taking into consideration the tetralin substitution, both in the 3-(tetralin-1-yl)propyl derivatives **35, 39, 42** and **46**, and in the 4-(tetralin-1-yl)butyl derivatives **36, 40, 43** and **47**, the highest σ_1 affinities and σ_1/σ_2 selectivities were obtained for 6-methoxy derivatives **42** and **43**, respectively ($K_i = 2.36$ and 2.12 nM; 73- and 117-fold, respectively). Therefore, the effect of the length of the intermediate alkyl chain was examined in the homologous series of 6-methoxytetralin derivatives **41**–**45**. It was evidenced that the presence of an alkyl chain of three to five methylene units results in high-affinity σ_1 ligands, four-membered compound **43** resulting as the most selective versus σ_2 receptor. In the corresponding 2,3-dihydro-5-methoxy-1*H*-indene series **30**–**33**, a five-methylene chain originated the most active and selective compound **32**. The enantiomers (*S*)-(+)-**39** and (*R*)-(−)-**39** and rac-emic **39** gave comparable

Table 2. σ Binding affinities and selectivities



Compound	R_1	R_2	R_3	m	n	K_i±SEM (nM)		K_i ratio
						σ_1	σ_2	σ_1/σ_2
23[a,b]	H	H	H	1	3	23.1±8.2	350±52	15
24	H	H	H	1	2	23.8±6.8	28.1±8.7	1
25	H	H	H	1	3	9.68±1.74	26.1±2.0	3
26	H	H	H	1	4	1.75±0.12	242±59	138
27	H	H	H	1	5	21.6±10.1	31.7±1.1	1.5
28	H	H	H	1	6	22.1±2.7	296±93	13
29	H	H	OCH_3	1	4	1.99±0.56	97.2±0.1	49
30	H	OCH_3	H	1	3	3.53±0.83	56.6±4.2	16
31	H	OCH_3	H	1	4	8.02±0.89	162±29	20
32	H	OCH_3	H	1	5	2.10±0.23	75.4±14.6	36
33	H	OCH_3	H	1	6	16.8±6.8	231±37	14
34	H	H	H	2	2	72.5±3.9	41.1±2.2	0.6
35	H	H	H	2	3	19.8±5.3	203±37	10
36	H	H	H	2	4	36.0±4.5	242±32	7
37[b]	H	H	H	2	5	20.0±3.2	318±86	16
38	H	H	H	2	6	17.5±2.3	369±35	21
(±)-**39**	H	H	OCH_3	2	3	20.0±5.9	206±67	10
(*S*)-(+)-**39**	H	H	OCH_3	2	3	11.6±2.1	219±16	19
(*R*)-(−)-**39**	H	H	OCH_3	2	3	33.2±10.6	174±2	5
40	H	H	OCH_3	2	4	2.71±0.77	183±62	68
41	H	OCH_3	H	2	2	7.64±0.85	88.7±14.0	12
42[b]	H	OCH_3	H	2	3	2.36±0.44	172±28	73
43[b]	H	OCH_3	H	2	4	2.12±0.30	247±52	117
44[b]	H	OCH_3	H	2	5	4.39±1.67	409±33	93
45	H	OCH_3	H	2	6	28.2±8.8	289±17	10
46	OCH_3	H	H	2	3	6.64±0.19	173±54	26
47	OCH_3	H	H	2	4	21.4±6.9	160±38	7
48	H	F	H	2	4	24.0±8.4	424±57[c]	18
49	H	F	H	2	5	3.97±1.37	155±20	39
SA4503[d]						0.012−0.48[e]	77.5±10.9	
BD1008[f]						1.72±0.49	82.8±17.2	48
NE100[g]						1.03±0.14	212±24	206
(+)-Pentazocine[b]						1.91±0.19		
DTG[b]							25.4±2.1	
Haloperidol						1.09±0.16		

[a]1*H*-inden-3-yl ($\Delta_{2,3}$).
[b]K_i data are simultaneously being published elsewhere.
[c](+)-SKF10047 was used to mask σ_1 receptors.
[d]Literature data: σ_1, IC_{50} = 17.4±1.9 nM; σ_2, IC_{50} = 1784±314 nM (ref 30).
[e]Three experiments' results falling in the reported range. In the other two experiments not dose-dependent curves were obtained, a plateau being observed in the concentration range of 10^{-10}–10^{-7} M.
[f]Literature data: σ_1, K_i = 2.2±0.65 nM; σ_2, K_i = 8.10±2.2 nM (ref 31).
[g]Literature data: σ_1, IC_{50} = 1.5 nM; σ_2, IC_{50} = 85 nM (ref 32).

K_i values both for σ_1 and σ_2 receptor affinity, so that no remarkable stereoselectivity was evidenced. Their absolute configurations were derived from a recent determination.[33] Fluorinated tetra-lin **49** demonstrated a good σ_1 affinity and selectivity; thus it can be proposed as a PET agent, when derivatized with ^{18}F. The σ_1 affinity of the most potent derivatives **26** and **43** was comparable to that of the reference compounds tested. All these compounds, except DTG, share structural features consisting in one basic nitrogen atom spaced by a five-membered chain from a phenyl ring. In this respect, NE 100 can be considered a cyclovinylogue. The lack of a second nitrogen or oxygen atom at a distance of two methylenes seems to enhance σ_1 versus σ_2 selectivity for our compounds, as well as for NE 100.

The restricted series of compounds tested at L-type Ca^{++} channel, including reference compounds, revealed moderate affinity (Table 3). The lowest K_i values, comparable to that of verapamil, were reached by (tetralin)pentyl derivatives **37** and **44**. High-affinity σ_1 ligands **26** and **32** also resulted as particularly selective versus this type of channel.

As it would be expected, for the tested compounds the σ_1 affinities joined up with high EBP affinities and in almost all cases surprisingly exceeded them, as it can be

Table 3. Other binding affinities and selectivities

Compound	$K_i \pm$SEM (nM)				K_i ratio
	L-type Ca^{++} channel	EBP	5-HT_{1A}[a]	MK 801[a]	σ_1/EBP
23	380±127[b]	3.85±0.60	7370		6
26	514±85	1.54±0.01			1.1
29	109±25.4				
32	1800±365	1.67±0.44			1.3
35	537±116	1.68±0.26			12
37	14.7±2.2[b]	2.48±1.23	3520	>917	8
(±)-**39**	229±48	0.50±0.10		>917	40
(*S*)-(+)-**39**	223±19	1.12±0.18		>917	10
(*R*)-(−)-**39**	170±61	1.03±0.13		>917	31
40	90.3±17.4	0.48±0.08			6
42	65.4±8.6[b]	0.57±0.02	9120		4
43	415±42[b]	0.67±0.19	>10,000	>917	3
44	20.8±6.6[b]	0.59±0.12	>10,000		7
46		0.76±0.14			9
49	253±34	14.8±3.7			0.3
SA 4503	156±15[c]	1.72±0.53	1810		
BD 1008	90.9±23.1	3.94±0.02			0.4
NE 100	87.5±12.2	14.6±4.1	1090		0.07
(±)-Verapamil	42.0±0.4[b]				
(±)-Ifenprodil		3.64±0.44			
8-OH-DPAT			1.73±0.10		
MK 801				3.49±0.27	

[a]Data without SEM are taken from one experiment.
[b]These K_i data are simultaneously being published elsewhere.
[c]Literature datum: 22.3% inhibition at 10 μM (ref 30).

seen from respective apparent K_i ratio (Table 3). Therefore, no highly selective σ_1/EBP ligand was found in this assay. Fluorinated compound **49** demonstrated the lowest affinity for EBP site ($K_i = 14.8$ nM) with a moderate selectivity σ_1/EBP. In contrast, compounds (±)-**39** and (−)-**39** showed the highest EBP selectivity versus σ_1 receptor (40- and 31-fold, respectively). Therefore, since most of the tested compounds bound at σ_1 receptor, they resulted mixed σ_1 and EBP ligands. The affinity towards EBP was enhanced by the presence of a methoxyl group in 5- or 6-position on the tetralin nucleus. Similarly, this situation occurs for SA 4503.

Finally, no considerable affinities were noticed at serotonin 5-HT_{1A} receptor and MK 801 site for the few tested compounds.

Conclusions

These 3,3-dimetilpiperidine derivatives are a new class of high-affinity σ_1 ligands. Besides, a significant σ_1 subtype selectivity was achieved in this class of compounds. Good results were obtained with an intermediate alkyl chain of four or five methylenes and a 6-methoxy-1,2,3,4-tetrahydronaphthalene nucleus, but the best ligand was the indane derivative **26**. The high flexibility of such a chain permits to fit in with the distance of the nitrogen atom and the phenyl ring, as in the pentazocine. A second intermediate nitrogen atom in the chain seems to be not essential for σ_1 affinity, but it enhances σ_2 affinity. These findings agree with the conclusions reported in the recent literature.[31] It is presumable that more rigid structures can separate EBP affinity from σ_1 affinity. However, if the belonging of σ_1 receptor to the EBP family will be confirmed by analogous functions in the sterol biosynthesis, inhibition of cholesterol formation and cell antiproliferative activity might be elicited also by σ_1 ligands and could be strengthened by mixed σ_1/EBP ligands.

Experimental

Chemistry

Column chromatography was performed with 1:30 ICN silica gel 60A (63–200 μm) as the stationary phase. Melting points were determined in open capillaries on a Gallenkamp electrothermal apparatus. Elemental analyses (C,H,N) were performed on a Carlo Erba model 1106 analyser. ^{1}H NMR spectra were recorded either on a Varian EM-390, where indicated 90 MHz (TMS as internal standard), or a Bruker AM 300 WB (300 MHz) instrument, with $CDCl_3$ as solvent; ^{13}C NMR were obtained on a Varian NMR 300 Mercury-VX (75 MHz) instrument; all values are reported in ppm (δ). Infrared spectra were recorded on a Perkin-Elmer, Spectrum one, FTIR. Recording of mass spectra was done on a HP 5995C gas chromatography/mass spectrometer, electron impact 70 eV, equipped with a HP59970A workstation; only significant *m*/*z* peaks, with their % relative intensity in parentheses, are herein reported. All spectra were in accordance with the assigned structures. All target compounds were transformed into their hydrochloride or hydrogen oxalate salts in the usual manner.

1-Benzyl-3,3-dimethylpiperidin-2,5-dione (2). 2,2-Dimethylglutaric acid (**1**) (15.0 g, 94 mmol) mixed with $SOCl_2$ (70 mL) was refluxed for 5 h, under stirring. Then the excess of $SOCl_2$ was removed under reduced pressure. To a solution of the acyl chloride in 1,2-dimethoxyethane (40 mL), was added dropwise a solution of

benzylamine (10.2 mL, 93 mmol) in the same solvent (20 mL) and the mixture was refluxed for 15 h, under stirring. Then the solvent was evaporated in vacuo and the crude residue was warmed for 8 h at 200 °C. The residue was chromatographed (petroleum ether/ethyl acetate 8:2, as eluent) to give **2** as a colorless oil in 74% yield. ^{1}H NMR (90 MHz) 1.25 (s, 6H, 2 CH_3), 1.80 (t, 2H, $J=6$ Hz, $(CH_3)_2CCH_2$), 2.72 (t, 2H, $J=6$ Hz, CH_2CO), 4.90 (s, 2H, benzylic), 7.25 (s, 5H, aromatic); IR (neat) 1724, 1679 cm^{-1}; GC/MS *m*/*z* 233 ($M^+ + 2$, 2), 232 ($M^+ + 1$, 21), 231 (M^+, 100), 188 (92), 146 (66).

1-Benzyl-3,3-dimethylpiperidine (3). A solution of imide **2** (16.0 g, 78 mmol) in anhydrous THF (200 mL) was added dropwise to a cooled suspension of $LiAlH_4$ (6.00 g, 0.16 mol) in the same solvent (200 mL). The mixture was refluxed for 24 h, under stirring. To the cooled suspension were added some drops of water to destroy the excess of the hydride. The mixture was filtered and the filtrate concentrated to dryness. The residue was taken up with CH_2Cl_2. This solution was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure to give the amine **3** as a colorless oil (12.6 g, 80% yield). ^{1}H NMR (90 MHz) 0.88 (s, 6H, 2 CH_3), 1.05–1.30 (m, 2H, $(CH_3)_2CCH_2$, 1.35–1.70 (m, 2H, piperidine CH_2), 1.95 (s, 2H, $NCH_2C(CH_3)_2$), 2.28 (t, 2H, $J=6$ Hz, CH_2N), 3.40 (s, 2H, benzylic), 7.15–7.45 (m, 5H, aromatic); IR (neat) 2794, 739, 698 cm^{-1}; GC/MS *m*/*z* 204 ($M^+ + 1$, 11), 203 (M^+, 65), 202 (50), 146 (27), 134 (75), 91 (100).

3,3-Dimethylpiperidine (4). 1-Benzyl-3,3-dimethylpiperidine (**3**) (12.6 g, 62 mmol) was dissolved in MeOH and hydrogenated at normal pressure and room temperature in the presence of 10% Pd/C (0.50 g) until the uptake ceased. The catalyst was removed by filtration through Celite® and the solvent was removed by distillation at normal pressure. The residue was fractionated by distillation at normal pressure (bp 105–108 °C; lit.[23] 136–138 °C), affording a colorless oil (3.8 g, 54% yield). ^{1}H NMR (90 MHz) 0.91 (s, 6H, 2 CH_3), 1.15–1.65 (m, 4H, $(CH_3)_2CCH_2CH_2$), 1.85 (s, 1H, NH, D_2O exchanged), 2.45 (s, 2H, $(CH_3)_2CCH_2NH$), 2.75 (t, 2H, $J=6$ Hz, CH_2CH_2NH); GC/MS *m*/*z* 114 ($M^+ + 1$, 6), 113 (M^+, 64), 98 (31), 57 (51), 44 (100).

2,3-Dihydro-1*H*-indene-1-acetic acid, Ethyl Ester (6a). This compound was chromatographed (petroleum ether/ethyl acetate, 99:1 as eluent) to give a colorless oil (88% yield). ^{1}H NMR (90 MHz) 1.25 (t, 3H, $J=6$ Hz, CH_3), 1.18–1.85 (m, 1H, *endo* CHH), 2.18–3.00 (m, 5H, *endo* CHH, benzylic CH_2 and CH_2CO), 3.35–3.78 (m, 1H, benzylic), 4.15 (q, 2H, $J=6$ Hz, OCH_2), 7.02–7.30 (m, 4H, aromatic); IR ($CHCl_3$) 1725 cm^{-1}; GC/MS *m*/*z* 204 (M^+, 48), 130 (48), 117 (100), 116 (74), 115 (45).

6-Methoxy-1,2,3,4-tetrahydronaphthalene-1-acetic acid, Ethyl Ester (6b). It was chromatographed, eluting with petroleum ether/ethyl acetate, 9:1, to give a colorless oil (43% yield). ^{1}H NMR (90 MHz) 1.30 (t, 3H, $J=9$ Hz, CH_3CH_2O), 1.65–2.10 (m, 4H, *endo* CH_2CH_2), 2.60–2.91 (m, 4H, benzylic CH_2 and CH_2CO), 3.10–3.52 (m, 1H, benzylic CH), 3.84 (s, 3H, OCH_3), 4.05–4.41 (m, 2H, OCH_2CH_3), 6.60–7.30 (m, 3H, aromatic); IR ($CHCl_3$) 1730 cm^{-1}; GC/MS *m*/*z* 249 ($M^+ + 1$, 5), 248 (M^+, 27), 174 (15), 161 (100).

2,3-Dihydro-1*H*-indene-1-ethanol (7a). The title compound was chromatographed using $CHCl_3/CH_3OH$ 9:1 as eluent to give a colorless oil (93% yield). ^{1}H NMR (90 MHz) 1.35–1.80 (m, 3H, *endo* CH_2 and OH, D_2O exchanged), 1.91–2.50 (m, 2H, $CHCH_2$), 2.65–2.98 (m, 2H, benzylic CH_2), 3.02–3.38 (m, 1H, benzylic CH), 3.77 (t, 2H, $J=6$ Hz, CH_2OH), 7.00–7.38 (m, 4H, aromatic); IR ($CHCl_3$) 3629, 1056 cm^{-1}; GC/MS *m*/*z* 163 ($M^+ + 1$, 5), 162 (M^+, 44), 144 (37), 129 (52), 117 (100), 115 (56).

6-Methoxy-1,2,3,4-tetrahydronaphthalene-1-ethanol (7b). It was chromatographed using CH_2Cl_2 as eluent to give a colorless oil (67% yield). ^{1}H NMR (90 MHz) 1.50–2.15 (m, 7H, $(CH_2)_2CHCH_2$ and OH, D_2O exchanged), 2.65–3.15 (m, 3H, benzylic), 3.70–4.00 and 3.87 (m + s, 5H, CH_2OH and CH_3), 6.65–7.35 (m, 3H, aromatic); GC/MS *m*/*z* 190 (83), 161 (17), 134 (100).

2,3-Dihydro-1*H*-indene-1-ethyl, methanesulfonate (8a). The crude residue was chromatographed (petroleum ether/ethyl acetate, 8:2, as eluent) to obtain the pure product as a white solide (65% yield). ^{1}H NMR (90 MHz) 1.55–2.13 (m, 2H, *endo* CH_2), 2.20–2.65 (m, 2H, $CHCH_2$), 2.85–3.12 (m, 5H, SO_2CH_3 and benzylic CH_2), 3.15–3.55 (m, 1H, benzylic CH), 4.49 (t, 2H, $J=6$ Hz, CH_2O), 7.19–7.45 (m, 4H, aromatic); GC/MS *m*/*z* 241 ($M^+ + 1$, 2), 240 (M^+, 16), 145 (18), 144 (93), 143 (21), 129 (100), 117 (85).

6-Methoxy-1,2,3,4-tetrahydronaphthalene-1-ethyl, methanesulfonate (8b). It was chromatographed, eluting with ethyl acetate/petroleum ether 8:2, to give a colorless oil (78% yield). ^{1}H NMR (90 MHz) 1.60–2.25 (m, 6H, $(CH_2)_2CHCH_2$), 2.60–2.90 (m, 2H, benzylic), 2.95–3.05 (m, 4H, SO_2CH_3 and benzylic CH), 3.81 (s, 3H, OCH_3), 4.35 (t, 2H, $J=6$ Hz, CH_2O), 6.60–7.25 (m, 3H, aromatic); IR ($CHCl_3$) 1380, 1173 cm$^{\pm 1}$; GC/MS *m*/*z* 285 ($M^+ + 1$, 7), 284 (M^+, 40), 162 (27), 161 (100), 160 (25).

Compounds 11a,b–16a,b. They were obtained as pure colorless oils by column chromatography (petroleum ether/CH_2Cl_2, 9:1 as eluent).

3-(4-Chlorobutyl)-1*H*-indene (11a). 25% yield; ^{1}H NMR 1.78–2.04 (m, 4H, $(CH_2)_2CH_2Cl$), 2.57–2.69 (m, 2H, allylic), 3.32–3.36 (m, 2H, benzylic), 3.59 (t, 2H, $J=7$ Hz, CH_2Cl), 6.23 (br t, 1H, vinylic), 7.21–7.48 (m, 4H, aromatic); GC/MS *m*/*z* 208 ($M^+ + 2$, 6), 207 ($M^+ + 1$, 3), 206 (M^+, 18), 130 (91), 129 (100), 128 (61), 115 (41).

3-(4-Chlorobutyl)-6-methoxy-1*H*-indene (11b). 18% yield; ^{1}H NMR 1.82–1.97 (m, 4H, $(CH_2)_2CH_2Cl$), 2.52–2.55 (m, 2H, CH_2 allylic), 3.28–3.29 (m, 2H, benzylic), 3.57 (t, 2H, $J=7$ Hz, CH_2Cl), 3.82 (s, 3H, CH_3), 6.07 (t, 1H, $J=2$ Hz, vinylic), 6.83–7.24 (m, 3H, aromatic); GC/MS *m*/*z* 238 ($M^+ + 2$, 9), 237 ($M^+ + 1$, 6), 236 (M^+, 27), 201 (29), 173 (30), 160 (100), 159 (48), 145 (28).

3-(5-Chloropentyl)-1*H*-indene (12a). 21% yield; ^{1}H NMR 1.51–1.89 (m, 6H, $(CH_2)_3CH_2Cl$), 2.54–2.61 (m, 2H, allylic), 3.30–3.34 (m, 2H, benzylic), 3.55 (t, 2H, $J=7$ Hz, CH_2Cl), 6.19–6.21 (m, 1H, vinylic), 7.16–7.47 (m, 4H, aromatic); GC/MS *m/z* 222 ($M^+ + 2$, 3), 221 ($M^+ + 1$, 1), 220 (M^+, 9), 130 (100), 129 (69), 128 (52), 115 (32).

3-(5-Chloropentyl)-6-methoxy-1*H*-indene (12b). 29% yield; ^{1}H NMR (90 MHz) 1.32–2.00 (m, 6H, $(CH_2)_3CH_2Cl$), 2.32–2.68 (m, 2H, allylic), 3.19–3.21 (m, 2H, benzylic), 3.52 (t, 2H, $J=7$ Hz, CH_2Cl), 3.85 (t, 3H, CH_3), 6.02 (br t, 1H, vinylic), 6.70–7.32 (m, 3H, aromatic); GC/MS *m/z* 252 ($M^+ + 2$, 4), 251 ($M^+ + 1$, 2), 250 (M^+, 13), 173 (21), 160 (100), 159 (26), 115 (33).

3-(6-Chlorohexyl)-1*H*-indene (13a). 56% yield; ^{1}H NMR (90 MHz) 1.28–2.00 (m, 8H, $(CH_2)_4CH_2Cl$), 2.47–2.75 (m, 2H, allylic), 3.32–3.47 (m, 2H, benzylic), 3.60 (t, 2H, $J=7$ Hz, CH_2Cl), 6.28–6.33 (m, 1H, vinylic), 7.19–7.61 (m, 4H, aromatic); GC/MS *m/z* 236 ($M^+ + 2$, 3), 235 ($M^+ + 1$, 2), 234 (M^+, 10), 130 (100), 129 (48), 128 (39), 115 (24).

3-(6-Chlorohexyl)-6-methoxy-1*H*-indene (13b). 26% yield; ^{1}H NMR (90 MHz) 1.27–2.00 (m, 8H, $(CH_2)_4CH_2Cl$), 2.55 (br t, 2H, allylic), 3.25–3.38 (m, 2H, benzylic), 3.55 (t, 2H, $J=7$ Hz, CH_2Cl), 3.88 (s, 3H, CH_3), 6.03–6.19 (m, 1H, vinylic), 6.80–7.35 (m, 3H, aromatic); GC/MS *m/z* 266 ($M^+ + 2$, 4), 265 ($M^+ + 1$, 2), 264 (M^+, 11), 160 (100), 159 (20), 115 (27).

4-(4-Chlorobutyl)-1,2-dihydro-7-fluoronaphthalene (14c). 30% yield; ^{1}H NMR (90 MHz) 1.56–1.97 (m, 4H, $(CH_2)_2CH_2Cl$), 2.00–2.51 (m, 4H, allylic), 2.70 (br t, 2H, benzylic), 3.52 (t, 2H, $J=7$ Hz, CH_2Cl), 5.78 (t, 1H, $J=5$ Hz, vinylic), 6.62–7.28 (m, 3H, aromatic); GC/MS *m/z* 240 ($M^+ + 2$, 5), 239 ($M^+ + 1$, 2), 238 (M^+, 16), 162 (73), 159 (22), 147 (100), 146 (53), 133 (24).

4-(5-Chloropentyl)-1,2-dihydro-7-fluoronaphthalene (15c). 17% yield; ^{1}H NMR (90 MHz) 1.20–1.97 (m, 6H, $(CH_2)_3CH_2Cl$), 2.04–2.54 (m, 4H, allylic), 2.59–2.91 (m, 2H, benzylic), 3.52 (t, 2H, $J=7$ Hz, CH_2Cl), 5.82 (br t, 1H, vinylic), 6.62–7.31 (m, 3H, aromatic); GC/MS *m/z* 254 ($M^+ + 2$, 3), 253 ($M^+ + 1$, 2), 252 (M^+, 10), 162 (100), 159 (21), 147 (78), 146 (51), 133 (24).

4-(6-Chlorohexyl)-1,2-dihydronaphthalene (16a). 24% yield; ^{1}H NMR (90 MHz) 1.10–2.01 (m, 8H, $(CH_2)_4CH_2Cl$), 2.21–2.58 (m, 4H, allylic), 2.61–3.00 (m, 2H, benzylic), 3.56 (br t, 2H, CH_2Cl), 5.88 (br t, 1H, vinylic), 7.01–7.48 (m, 4H, aromatic); GC/MS *m/z* 250 ($M^+ + 2$, 3), 249 ($M^+ + 1$, 2), 248 (M^+, 9), 144 (100), 129 (80), 128 (51), 115 (24).

4-(6-Chlorohexyl)-1,2-dihydro-7-methoxynaphthalene (16b). 33% yield; ^{1}H NMR (90 MHz) 1.20–1.83 (m, 8H, $(CH_2)_4CH_2Cl$), 2.00–2.51 (m, 4H, allylic), 2.67 (br t, 2H, benzylic), 3.44 (t, 2H, $J=7$ Hz, CH_2Cl), 3.79 (s, 3H, CH_3), 5.68 (br t, 1H, vinylic), 6.62–7.23 (m, 3H, aromatic); GC/MS *m/z* 280 ($M^+ + 2$, 4), 279 ($M^+ + 1$, 2), 278 (M^+, 12), 174 (100), 159 (25).

Compounds 17a,b–22a,b. These compounds were obtained as colorless oils in the 90–99% yields.

1-(4-Chlorobutyl)-2,3-dihydro-1*H*-indene (17a). ^{1}H NMR 1.38–2.04 (m, 7H, C*H*HCH$(CH_2)_3$), 2.27–2.38 (m, 1H, CH*H*CH), 2.78–3.29 (m, 3H, benzylic), 3.60 (t, 2H, $J=7$ Hz, CH_2Cl), 7.11–7.27 (m, 4H, aromatic); GC/MS *m/z* 210 ($M^+ + 2$, 2), 209 ($M^+ + 1$, 1), 208 (M^+, 7), 117 (100), 115 (24).

1-(4-Chlorobutyl)-2,3-dihydro-5-methoxy-1*H*-indene (17b). ^{1}H NMR 1.32–1.86 (m, 7H, C*H*HCH$(CH_2)_3$), 2.22–2.33 (m, 1H, CH*H*CH), 2.73–3.07 (m, 3H, benzylic), 3.55 (t, 2H, $J=7$ Hz, CH_2Cl), 3.77 (s, 3H, CH_3), 6.68–7.08 (m, 3H, aromatic); GC/MS *m/z* 240 ($M^+ + 2$, 2), 239 ($M^+ + 1$, 1), 238 (M^+, 8), 147 (100).

1-(5-Chloropentyl)-2,3-dihydro-1*H*-indene (18a). ^{1}H NMR 1.39–1.91 (m, 9H, C*H*HCH$(CH_2)_4$), 2.24–2.35 (m, 1H, CH*H*CH), 2.78–3.16 (m, 3H, benzylic), 3.56 (t, 2H, $J=7$ Hz, CH_2Cl), 7.12–7.25 (m, 4H, aromatic); GC/MS *m/z* 224 ($M^+ + 2$, 2), 223 ($M^+ + 1$, 1), 222 (M^+, 6), 117 (100), 115 (22).

1-(5-Chloropentyl)-2,3-dihydro-5-methoxy-1*H*-indene (18b). ^{1}H NMR 1.38–1.89 (m, 9H, C*H*HCH$(CH_2)_4$), 2.21–2.32 (m, 1H, CH*H*CH), 2.73–3.06 (m, 3H, benzylic), 3.52 (t, 2H, $J=7$ Hz, CH_2Cl), 3.77 (s, 3H, CH_3), 6.68–7.08 (m, 3H, aromatic); GC/MS *m/z* 254 ($M^+ + 2$, 2), 253 ($M^+ + 1$, 1), 252 (M^+, 5), 147 (100).

1-(6-Chlorohexyl)-2,3-dihydro-1*H*-indene (19a). ^{1}H NMR (90 MHz) 1.18–1.98 (m, 11H, C*H*HCH$(CH_2)_5$), 2.01–2.44 (m, 1H, CH*H*CH), 2.70–3.18 (m, 3H, benzylic), 3.46 (t, 2H, $J=7$ Hz, CH_2Cl), 7.07–7.35 (m, 4H, aromatic); GC/MS *m/z* 238 ($M^+ + 2$, 2), 237 ($M^+ + 1$, 1), 236 (M^+, 7), 117 (100), 115 (23).

1-(6-Chlorohexyl)-2,3-dihydro-5-methoxy-1*H*-indene (19b). ^{1}H NMR (90 MHz) 1.22–1.98 (m, 11H, C*H*HCH$(CH_2)_5$), 2.06–2.48 (m, 1H, CH*H*CH), 2.69–3.18 (m, 3H, benzylic), 3.52 (t, 2H, $J=7$ Hz, CH_2Cl), 3.80 (s, 3H, CH_3), 6.62–7.18 (m, 3H, aromatic); GC/MS *m/z* 268 ($M^+ + 2$, 3), 267 ($M^+ + 1$, 2), 266 (M^+, 8), 147 (100).

1-(4-Chlorobutyl)-6-fluoro-1,2,3,4-tetrahydronaphthalene (20c). ^{1}H NMR (90 MHz) 1.33–2.04 (m, 10H, $(CH_2)_2CH(CH_2)_3$), 2.61–2.89 (m, 3H, benzylic), 3.58 (t, 2H, $J=7$ Hz, CH_2Cl), 6.70–7.33 (m, 3H, aromatic); GC/MS *m/z* 242 ($M^+ + 2$, 2), 241 ($M^+ + 1$, 1), 240 (M^+, 5), 149 (100), 109 (18).

1-(5-Chloropentyl)-6-fluoro-1,2,3,4-tetrahydronaphthalene (21c). ^{1}H NMR (90 MHz) 1.23–2.05 (m, 12H, $(CH_2)_2CH(CH_2)_4$), 2.52–2.93 (m, 3H, benzylic), 3.57 (t, 2H, $J=7$ Hz, CH_2Cl), 6.70–7.30 (m, 3H, aromatic); GC/MS *m/z* 256 ($M^+ + 2$, 1), 255 ($M^+ + 1$, 1), 254 (M^+, 4), 149 (100), 109 (21).

1-(6-Chlorohexyl)-1,2,3,4-tetrahydronaphthalene (22a). ^{1}H NMR (90 MHz) 0.78–1.90 (m, 14H, $(CH_2)_2CH(CH_2)_5$), 2.57–2.91 (m, 3H, benzylic), 3.51 (t, 2H, $J=7$ Hz, CH_2Cl), 7.01–7.20 (m, 4H, aromatic); GC/MS *m/z* 252 ($M^+ + 2$, 2), 251 ($M^+ + 1$, 1), 250 (M^+, 5), 131 (100), 91 (20).

1-(6-Chlorohexyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (22b). ^{1}H NMR (90 MHz) 1.22–1.98 (m, 14H, $(CH_2)_2CH(CH_2)_5$), 2.57–2.88 (m, 3H, benzylic), 3.52 (t, 2H, $J=7$ Hz, CH_2Cl), 3.80 (s, 3H, CH_3), 6.60–7.20 (m, 3H, aromatic); GC/MS m/z 282 ($M^+ + 2$, 1), 281 ($M^+ + 1$, 1), 280 (M^+, 4), 161 (100).

1-[2-(2,3-Dihydro-1*H*-inden-1-yl)ethyl]-3,3-dimethylpiperidine (24). ^{1}H NMR 0.94 (s, 6H, $2CH_3$), 1.15–1.35 (m, 2H, $CH_2C(CH_3)_2$), 1.50–1.78 (m, 4H, piperidine CH_2 and *endo* CH_2), 1.95–2.19 (m, 3H, $CHCH_2$ and $NCHHC(CH_3)_2$), 2.20–2.45 (m, 5H, CH_2NCH_2 and $NCHHC(CH_3)_2$), 2.75–3.02 (m, 2H, benzylic CH_2), 3.07–3.20 (m, 1H, benzylic CH), 7.05–7.32 (m, 4H, aromatic); GC/MS m/z 258 ($M^+ + 1$, 10), 257 (M^+, 43), 127 (25), 126 (100), 115 (20).

1-[4-(2,3-Dihydro-1*H*-inden-1-yl)butyl]-3,3-dimethylpiperidine (26). ^{1}H NMR 0.95 (s, 6H, 2 CH_3), 1.22 (t, 2H, $J=6$ Hz, $CH_2C(CH_3)_2$), 1.35–1.90 (m, 9H, $CH(CH_2)_3$, piperidine CH_2 and *endo* CHH), 2.03 (br s, 2H, $NCH_2C(CH_3)_2$), 2.21–2.32 (m, 5H, CH_2NCH_2, *endo* CHH), 2.76–3.13 (m, 3H, benzylic), 7.10–7.22 (m, 4H, aromatic); ^{13}C NMR 22.95, 25.88, 27.46, 27.83, 30.99, 31.70, 32.42, 35.23, 37.96, 45.10, 55.41, 59.36, 66.38, 123.82, 124.65, 122.23, 126.42, 144.28, 148.00; GC/MS m/z 286 ($M^+ + 1$, 1), 285 (M^+, 6), 126 (100), 117 (20).

1-[5-(2,3-Dihydro-1*H*-inden-1-yl)pentyl]-3,3-dimethylpiperidine (27). ^{1}H NMR 0.95 (s, 6H, 2 CH_3), 1.22 (t, 2H, $J=6$ Hz, $CH_2C(CH_3)_2$), 1.29–1.88 (m, 11H, $CH(CH_2)_4$, piperidine CH_2 and *endo* CHH), 2.04 (br s, 2H, $NCH_2C(CH_3)_2$), 2.20–2.31 (m, 5H, CH_2NCH_2 and *endo* CHH), 2.21–3.12 (m, 3H, benzylic), 7.10–7.22 (m, 4H, aromatic); GC/MS m/z 300 ($M^+ + 1$, 1), 299 (M^+, 6), 126 (100), 117 (18).

1-[6-(2,3-Dihydro-1*H*-inden-1-yl)hexyl]-3,3-dimethylpiperidine (28). ^{1}H NMR 0.94 (s, 6H, 2 CH_3), 1.21–1.84 (m, 15H, $CH(CH_2)_5$, piperidine CH_2CH_2 and *endo* CHH), 2.01 (br s, 2H, $NCH_2C(CH_3)_2$), 2.15–2.30 (m, 5H, CH_2NCH_2 and *endo* CHH), 2.74–3.08 (m, 3H, benzylic), 7.09–7.24 (m, 4H, aromatic); GC/MS m/z 314 ($M^+ + 1$, 2), 313 (M^+, 7), 126 (100), 117 (18).

1-[4-(2,3-Dihydro-5-methoxy-1*H*-inden-1-yl)butyl]-3,3-dimethylpiperidine (31). ^{1}H NMR 0.92 (s, 6H, 2 CH_3), 1.19 (t, 2H, $J=6$ Hz, $CH_2C(CH_3)_2$), 1.34–1.82 (m, 9H, $CH(CH_2)_3$, piperidine CH_2 and *endo* CHH), 2.00 (br s, 2H, $NCH_2C(CH_3)_2$), 2.20–2.31 (m, 5H, CH_2NCH_2 and *endo* CHH), 2.74–3.03 (m, 3H, benzylic), 3.76 (s, 3H, OCH_3), 6.67–7.07 (m, 3H, aromatic); GC/MS m/z 316 ($M^+ + 1$, 4), 315 (M^+, 18), 126 (100).

1-[5-(2,3-Dihydro-5-methoxy-1*H*-inden-1-yl)pentyl]-3,3-dimethylpiperidine (32). ^{1}H NMR 0.92 (s, 6H, 2 CH_3), 1.19 (t, 2H, $J=6$ Hz, $CH_2C(CH_3)_2$), 1.24–1.81 (m, 11H, $CH(CH_2)_4$, piperidine CH_2 and *endo* CHH), 1.99 (br s, 2H, $NCH_2C(CH_3)_2$), 2.20–2.31 (m, 5H, CH_2NCH_2 and *endo* CHH), 2.71–3.04 (m, 3H, benzylic), 3.76 (s, 3H, OCH_3), 6.67–7.08 (m, 3H, aromatic); ^{13}C NMR 22.88, 27.18, 27.86, 28.08, 30.92, 31.87, 32.84, 35.59, 37.89, 44.23, 55.39, 55.61, 59.46, 66.31, 110.07, 112.01, 124.25, 140.19, 145.77, 158.81; GC/MS m/z 330 ($M^+ + 1$, 2), 329 (M^+, 7), 147 (16), 126 (100).

1-[6-(2,3-Dihydro-5-methoxy-1*H*-inden-1-yl)hexyl]-3,3-dimethylpiperidine (33). ^{1}H NMR 0.97 (s, 6H, 2 CH_3), 1.25–1.79 (m, 15H, $CH(CH_2)_5$, piperidine CH_2CH_2 and *endo* CHH), 1.85–2.30 (m, 7H, $NCH_2C(CH_3)_2$, CH_2NCH_2 and *endo* CHH), 2.71–3.35 (m, 3H, benzylic), 3.76 (s, 3H, OCH_3), 6.67–7.24 (m, 3H, aromatic); GC/MS m/z 344 ($M^+ + 1$, 5), 343 (M^+, 21), 126 (100).

3,3-Dimethyl-1-[6-(1,2,3,4-tetrahydronaphthalen-1-yl)-hexyl]piperidine (38). ^{1}H NMR 0.95 (s, 6H, 2 CH_3), 1.17–1.89 (m, 18H, $(CH_2)_2CH(CH_2)_5$ and piperidine CH_2CH_2), 1.90–2.49 (m, 6H, CH_2NCH_2 e $NCH_2C(CH_3)_2$), 2.71–2.74 (m, 3H, benzylic), 7.01–7.15 (m, 4H, aromatic); GC/MS m/z 328 ($M^+ + 1$, 3), 327 (M^+, 11), 126 (100).

3,3-Dimethyl-1-[2-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl]piperidine (41). ^{1}H NMR 0.94 (2 s, 6H, 2 CH_3), 1.15–1.25 (m 2H, $CH_2C(CH_3)_2$), 1.45–1.74 (m, 6H, *endo* CH_2CH_2 and piperidine CH_2), 1.75–1.88 (m, 2H, $CHCH_2$), 1.89–2.15 (m, 2H, $NCH_2C(CH_3)_2$), 2.20–2.45 (m, 4H, CH_2NCH_2), 2.65–2.85 (m, 3H, benzylic), 3.75 (s, 3H, OCH_3), 6.65–7.12 (m, 3H, aromatic); GC/MS m/z 302 ($M^+ + 1$, 8), 301 (M^+, 33), 160 (20), 126 (100).

3,3-Dimethyl-1-[4-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)butyl]piperidine (43). This compound has been already characterized[20] by ^{1}H NMR and GC/MS; ^{13}C NMR 20.07, 22.78, 25.44, 27.23, 27.83, 30.36, 30.95, 37.04, 37.12, 37.83, 55.29, 55.39, 59.29, 66.19, 112.05, 113.64, 129.69, 133.99, 138.43, 157.43.

3,3-Dimethyl-1-[6-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)hexyl]piperidine (45). ^{1}H NMR 0.97 (s, 6H, 2 CH_3), 1.23–1.84 (m, 18H, $(CH_2)_2CH(CH_2)_5$ and piperidine CH_2CH_2), 1.85–2.64 (m, 6H, CH_2NCH_2 e $NCH_2C(CH_3)_2$), 2.65–2.71 (m, 3H, benzylic), 3.74 (s, 3H, OCH_3), 6.56–7.24 (m, 3H, aromatic); GC/MS m/z 358 ($M^+ + 1$, 4), 357 (M^+, 14), 126 (100).

3,3-Dimethyl-1-[4-(6-fluoro-1,2,3,4-tetrahydronaphthalen-1-yl)butyl]piperidine (48). ^{1}H NMR 0.92 (s, 6H, 2 CH_3), 1.19 (br t, 2H, $CH_2C(CH_3)_2$), 1.28–1.84 (m, 12H, $(CH_2)_2CH(CH_2)_3$ and piperidine CH_2), 1.99 (s, 2H, $NCH_2C(CH_3)_2$), 2.22–2.26 (m, 4H, CH_2NCH_2), 2.70–2.72 (m, 3H, benzylic), 6.70–7.24 (m, 3H, aromatic); GC/MS m/z 318 ($M^+ + 1$, 1), 317 (M^+, 5), 149 (15), 126 (100), 109 (15).

3,3-Dimethyl-1-[5-(6-fluoro-1,2,3,4-tetrahydronaphthalen-1-yl)pentyl]piperidine (49). ^{1}H NMR 0.92 (s, 6H, 2 CH_3), 1.19 (t, 2H, $J=6$ Hz, $CH_2C(CH_3)_2$), 1.25–1.88 (m, 14H, $(CH_2)_2CH(CH_2)_4$ and piperidine CH_2), 2.00 (s, 2H, $NCH_2C(CH_3)_2$), 2.15–2.24 (m, 4H, CH_2NCH_2), 2.68–2.75 (m, 3H, benzylic), 6.70–7.24 (m, 3H, aromatic); ^{13}C NMR 19.68, 22.89, 27.17, 27.46, 27.56, 27.77, 28.01, 30.08, 30.92, 37.16, 37.22, 37.91, 55.35, 59.40, 66.36, 112.51, 112.78, 115.03, 115.29, 130.05, 130.16, 137.36, 139.18, 139.28, 162.49; GC/MS m/z 332 ($M^+ + 1$, 2), 331 (M^+, 9), 149 (15), 126 (100).

Radioligand binding assays

σ_1 Binding. The σ_1 receptor affinities were determined as described by Matsumoto et al.[34] with minor modifications. Briefly, in a total volume of 1.0 mL of 50 mM Tris·HCl, pH 8.0, were suspended guinea-pig brain membranes, 1.7 nM (+)-[^{3}H]-pentazocine and the drug studied or reference compound (six to nine concentrations). Incubation at room temperature for 120 min was terminated with 1 mL of ice-cold 50 mM Tris·HCl, pH 8.0 and vacuum filtration through GF/B filters that were presoaked in 0.5% PEI for 60 min. The filters were washed twice with ice-cold buffer. The non specific binding was defined in the presence of (+)-pentazocine 1 μM. The K_d (2.89 nM) and B_{max} (540 fmol/mg of protein) were determined in a Scatchard experiment.

σ_2 Binding. Affinities for σ_2 receptor were determined as described by Matsumoto et al.[34] with minor modifications. Briefly, in a total volume of 1.0 mL of 50 mM Tris·HCl, pH 8.0, were suspended rat liver membranes, 2.5 nM [^{3}H]-DTG, 1 μM (+)-pentazocine, the drug studied or reference compound (six to nine concentrations). Incubation at room temperature for 120 min was terminated with 1 mL of ice-cold 50 mM Tris·HCl, pH 8.0 and vacuum filtration through GF/B filters that were presoaked in 0.5% PEI for 60 min. The filters were washed twice with ice-cold buffer. The non specific binding was defined in the presence of 10 μM DTG. The K_d (10.4 nM) and B_{max} (1520 fmol/mg of protein) were determined in a Scatchard experiment.

L-Type Ca^{++} channel binding. The Ca^{++} channel affinities were determined as described by Reynolds et al.[35] with minor modifications. In a total volume of 1.0 mL of 50 mM Hepes, pH 7.4, were suspended rat brain membranes, 0.2 nM (−)-[^{3}H]-desmethoxyverapamil, the drug or reference compound (six to nine concentrations). Incubation at room temperature for 60 min was terminated by rapid filtration on GF/C filters which were washed twice with 1 mL of ice-cold buffer. The non specific binding was defined in the presence of 10 μM (±)-verapamil. The K_d value used for (−)-[^{3}H]-desmethoxyverapamil was 0.55 nM.

EBP site binding. The EBP receptor affinities were determined as described by Moebius et al.[36] with minor modifications. In a total volume of 1.0 mL of buffer (0.1 w/v digitonin, 10 mM Tris·HCl, 0.1 mM PMFS, pH 7.4), were suspended guinea-pig liver membranes, 0.5 nM (±)-[^{3}H]-emopamil, the drug or reference compound (six to nine concentrations). Incubation at room temperature for 60 min was terminated with 3 mL of ice-cold buffer (10% w/v PEG 6000, 10 mM Tris·HCl, 10 mM $MgCl_2$) pH 7.4 and vacuum filtration through GF/C filters that were presoaked in PEI 0.5% for 20 min. The filters were washed with 3 mL of ice-cold buffer. The non specific binding was defined in the presence of 1 μM ifenprodil. The K_d value used was 4.4 nM.

5-HT_{1A} serotonergic binding. The 5-HT_{1A} receptor affinities were determined as described by Borsini et al.[37] with minor modifications. In a total volume of 1.0 mL of 50 mM Tris·HCl, pH 7.6, were suspended hippocampus membranes, 1.0 nM [^{3}H]-8-OH-DPAT, the drug or reference compound (six to nine concentrations). Incubation at 37 °C for 20 min was terminated by rapid filtration on GF/B filters which were washed twice with 3 mL of ice-cold buffer. The non specific binding was defined in the presence of 1.0 μM 8-OH-DPAT. The K_d value used for 8-OH-DPAT was 8.8 nM.

MK 801 site binding. The MK 801 receptor affinities were determined as described by Bergeron et al.[38] with minor modifications. In a total volume of 1.0 mL of 5 mM Tris·HCl, pH 7.7 were suspended rat brain membranes, 2 nM [^{3}H]-MK 801, 100 μM D-glutamic acid, 100 μM L-glycine, the drug or reference compound (six to nine concentrations). Incubation at room temperature for 60 min was terminated by rapid filtration on GF/B filters, which were washed by three×4.0 mL of ice-cold buffer. The non specific binding was defined in the presence of 1 μM MK 801. The K_d value used for MK 801 was 11 nM.

Acknowledgements

This study was supported by research grant no. 9903108895-005 from Università degli Studi di Bari and MURST (Italy) for the scientific program in C07X field-2000–2002: 'Arylpiperazine derivatives: structural modifications to modulate their activity toward some C.N.S. receptors, 5-HT1A, D2, D4, sigma-1 and sigma-2, involved in pathological events such as depression, schizophrenia and Alzheimer'.

References

1. Snyder, S. H.; Largent, B. L. *J. Neuropsychiatry Clin. Neurosci.* **1989**, *1*, 7.
2. Guitart, X.; Farré, A. J. *Eur. J. Pharmacol.* **1998**, *363*, 127.
3. Takahashi, S.; Sonehara, K.; Takagi, K.; Miwa, T.; Horikomi, K.; Mita, N.; Nagase, H.; Iizuka, K.; Sakai, K. *Psychopharmacology* **1999**, *145*, 295.
4. Oshiro, Y.; Sakurai, Y.; Sato, S.; Kurahaschi, N.; Tanaka, T.; Kikuchi, T.; Tottori, K.; Uwahodo, Y.; Miwa, T.; Nishi, T. *J. Med. Chem.* **2000**, *43*, 177.
5. Maurice, T.; Lockhart, B. P. *Prog. Neuro-Psychopharmacol. Biol. Psychiat.* **1997**, *21*, 69.
6. McCraken, K. A.; Bowen, W. D.; de Costa, B. R.; Matsumoto, R. R. *Eur. J. Pharmacol.* **1999**, *370*, 225.
7. De Loore, K. L.; Lesage, A. S.; Peeters, L.; Leysen, J. E. *Neurosci. Res. Comm.* **1994**, *14*, 43.
8. Abou-Garbia, M.; Ablordeppey, S. Y.; Glennon, R. A. *Ann. Rep. Med. Chem.* **1993**, *28*, 1.
9. Vilner, B. J.; John, C. S.; Bowen, W. D. *Cancer Res.* **1995**, *55*, 408.
10. Ishiwata, K.; Noguchi, J.; Ishii, S.; Hatano, K.; Ito, K.; Nabeshima, T.; Senda, M. *Nucl. Med. Biol.* **1998**, *25*, 195.
11. Quirion, R.; Bowen, W. D.; Itzhak, Y.; Junien, J. L.; Musacchio, J. M.; Rothman, R. B.; Su, T.-P.; Tam, S. W.; Taylor, D. P. *Trends Pharmacol. Sci.* **1992**, *13*, 85.
12. Bowen, W. D. *Pharm. Acta Helv.* **2000**, *74*, 211.
13. Debonnel, G.; Montigny, C. *Life Sci.* **1996**, *58*, 721.
14. Vilner, B. J.; Bowen, W. D. *J. Pharmacol. Exp. Ther.* **2000**, *292*, 900.

15. Carroll, F. I.; Bai, X.; Dehghani, A.; Mascarella, S. W.; Williams, W.; Bowen, W. D. *J. Med. Chem.* **1999**, *42*, 4621.
16. de Costa, B. R.; He, X.-S. In *Sigma Receptors*; Itzhak, Y., Ed.; Academic: London, 1994; pp 45–111.
17. Kekuda, R.; Prasad, P. D.; Fei, Y. J.; Leibach, F. H.; Ganapathy, V. *Biochem. Biophys. Res. Comm.* **1996**, *229*, 553.
18. Moebius, F. F.; Striessnig, J.; Glossmann, H. *Trends Pharmacol. Sci.* **1997**, *18*, 67.
19. Hanner, M.; Moebius, F. F.; Weber, F.; Grabner, M.; Striessnig, J.; Glossmann, H. *J. Biol. Chem.* **1995**, *270*, 7551.
20. Berardi, F.; Santoro, S.; Perrone, R.; Tortorella, V.; Govoni, S.; Lucchi, L. *J. Med. Chem.* **1998**, *41*, 3940.
21. Franco, P.; Ferri, N.; Perrone, R.; Berardi, F.; Govoni, S.; Fumagalli, R.; Corsini, A. *Pharmacol. Res.* **1999**, *39*(Suppl.), 70.
22. Moebius, F.; Reiter, R. J.; Bermoser, K.; Glossmann, H.; Cho, S. Y.; Paik, Y.-K. *Mol. Pharmacol.* **1998**, *54*, 591.
23. Von Hoch, D.; Karrer, P. *Helv. Chim. Acta* **1954**, *37*, 397.
24. Perrone, R.; Berardi, F.; Colabufo, N. A.; Leopoldo, M.; Tortorella, V.; Fornaretto, M. G.; Caccia, C.; McArthur, R. A. *J. Med. Chem.* **1996**, *39*, 4928.
25. Berardi, F.; Giudice, G.; Perrone, R.; Tortorella, V.; Govoni, S.; Lucchi, L. *J. Med. Chem.* **1996**, *39*, 4255.
26. Owton, W. M.; Brunavs, M. *Synth. Comm.* **1991**, *21*, 981.
27. Fujimura, K.; Matsumoto, J.; Niwa, M.; Kobayashi, T.; Kawashima, Y.; In, Y.; Ishida, T. *Bioorg. Med. Chem.* **1997**, *5*, 1675.
28. de Costa, B. R.; Radesca, L.; Di Paolo, L.; Bowen, W. D. *J. Med. Chem.* **1992**, *35*, 38.
29. Nakazato, A.; Otha, K.; Sekiguchi, Y.; Okuyama, S.; Chaki, S.; Kawashima, Y.; Hatayama, K. *J. Med. Chem.* **1999**, *42*, 1076.
30. Matsuno, K.; Nakazawa, M.; Okamoto, K.; Kawaschima, Y.; Mita, S. *Eur. J. Pharmacol.* **1996**, *306*, 271.
31. Maeda, D. Y.; Williams, W.; Bowen, W. D.; Coop, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 17.
32. Nakazato, A.; Kumagai, T.; Otha, K.; Chaki, S.; Okuyama, S.; Tomisawa, K. *J. Med. Chem.* **1999**, *42*, 3965.
33. Perrone, R.; Berardi, F.; Colabufo, N. A.; Leopoldo, M.; Tortorella, V. *J. Med. Chem.* **1999**, *42*, 490.
34. Matsumoto, R. R.; Bowen, W. D.; Tom, M. A.; Nhi Vo, V.; Truong, D. D.; de Costa, B. R. *Eur. J. Pharmacol.* **1995**, *280*, 301.
35. Reynolds, B. J.; Snowman, A. M.; Snyder, S. H. *J. Pharmacol. Exp. Ther.* **1986**, *237*, 731.
36. Moebius, F. F.; Hanner, M.; Knaus, H. G.; Weber, F.; Striessnig, J.; Glossmann, H. *J. Biol. Chem.* **1994**, *269*, 29314.
37. Borsini, F.; Giraldo, E.; Monferini, E.; Antonini, G.; Parenti, M.; Bietti, G.; Donetti, A. *Naunyn. Schmiedebergs Arch. Pharmacol.* **1995**, *352*, 276.
38. Bergeron, R. J.; Weimar, W. R.; Wu, Q.; Feng, Y.; McManis, J. S. *J. Med. Chem.* **1996**, *39*, 5257.