New Adamantane Derivatives with Sigma Affinity and Antiproliferative Activity

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Abstract: The synthesis of 4-(1-adamantyl)-4,4-diarylbutylamines **1**, 5-(1-adamantyl)-5,5-diarylpentylamines **2** and 6-(1-adamantyl)-6,6-diarylhexylamines **3** is described and the σ1, σ2-receptors and sodium channels binding affinity of compounds **1** were investigated. The *in vitro* activity of compounds **1**, **2** and **3** against main cancer cell lines is significant. One of the most active analogs, **1a**, had an interesting *in vivo* anticancer profile against the ovarian cancer cell line IGROV-1, which was associated with an anagelsic activity against the neuropathic pain induced by the main anticancer drugs.

Keywords: Diaryladamantanealkanamines, synthesis, sigma-receptors affinity, sodium channels affinity, anti-proliferative activity, *in vivo* anticancer profile.

INTRODUCTION

Sigma (σ) receptors have been recently involved in anticancer activity. Even though, they have been considered as opioid receptors, the sigma receptors were classified as a distinct pharmacological entity and their function was unrelated to the function of the opioid receptors [1-3]. Based on the ligand selectivity in the binding assays, two subtypes, the sigma-1 (σ1) and the sigma-2 (σ2) receptors, were identified [2-4]. The σ1 receptor was cloned, firstly in 1996 [5], while σ2 receptor has not been cloned until now [2,3]. σ1 and σ2 receptors have recently been implicated in the programmed cell death (apoptosis) [3,6-10]. Indeed, σ1 and σ2 receptors are highly expressed in cancer cells and up-regulated prior to mitosis [11,12] suggesting important cellular functions in cancer and putative anticancer activity for σ1 antagonists [13,14] or σ2 agonists [8-10]. The former deactivate the σ1 receptor activity, which is anti-apoptotic and neuroprotective [3,6,15-17] and the latter stimulate the receptor activity, which induces or, more likely, sensitizes cancer cells for apoptosis [8,9,18]. Although there is considerable evidence of antiproliferative and cytotoxic activity for σ1 antagonists, σ2 putative agonists and mixed σ1/σ2 ligands [7-10,13], the mechanism of their action is not yet fully clarified. Indeed, in spite of a relative clarification of the pro-apoptotic effects of σ1 antagonists [3,6,13] more, other than mitochondrion-associated ER membrane (MAM) and caspases pathways, seems to be implicated in the σ1 receptor mediated apoptosis of cancer cells [3,7]. Otherwise, in spite of caspases-independent apoptosis pathways proposed for σ2 agonists [8], anticancer activity and caspases-dependent apoptosis of cancer cells were found recently for σ2 specific ligands [9]. Moreover, in relation to the apoptotic pathways, there is evidence, that the sigma receptors modulate ion channels [2,3,19,20], such as Ca^{2+}, K^+, Cl^- and more importantly, in relation to metastasis of cancer cells, the voltage-gated Na^+ channel [21,22]. Finally, they regulate the apoptotic processes by binding to the cholesterol in the lipid rafts [23,24]. These indications might enlighten the anticancer potency of sigma ligands. SAR studies prove that the presence of a hydrophobic aryl or cycloalkyl ring linked to amine via a carbon chain of 3-5 atoms, which might include a heteroatom, is an essential structural requirement for affinity at the (σ) receptors [25-26].

In the course of our program directed towards the synthesis of aminoadamantane derivatives with pharmacological interest, we designed 4-(1-adamantyl)-4,4-diarylbutylamines **1**, 5-(1-adamantyl)-5,5-diarylpentylamines **2** and 6-(1-adamantyl)-6,6-diarylhexylamines **3**. These include into their scaffold two aromatic rings and a hydrophobic adamantane moiety linked to an amine nitrogen atom. Compounds **1** were investigated for binding affinity at both σ1, σ2 receptors and Na^+ channels. All the new compounds were evaluated *in vitro* for the antiproliferative and cytotoxic activity in cancer and normal cell lines and one of them (**1a**), in one xenograft (ovarian).

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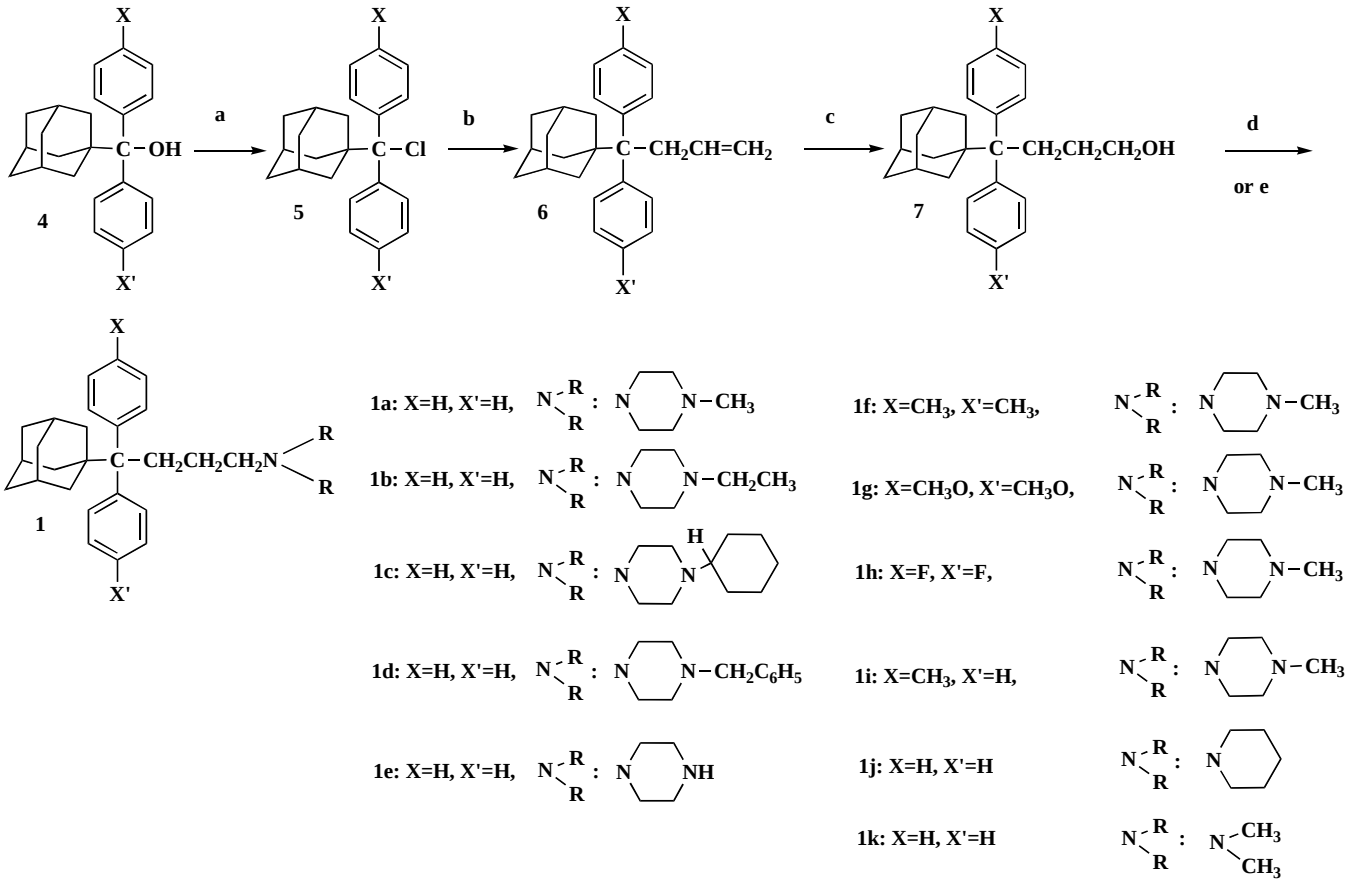
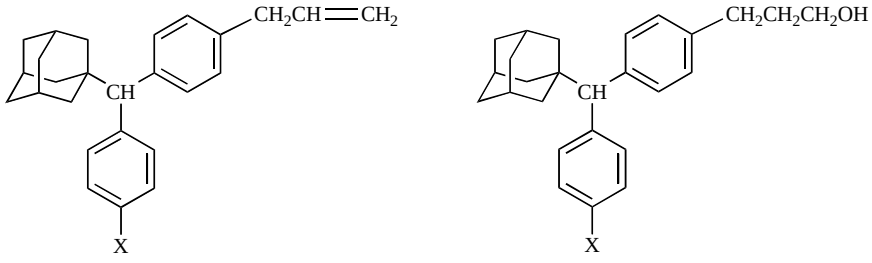


Scheme 1. Reagents and conditions: a) $SOCl_2/CH_3COCl$, reflux for 30 min; b) $CH_2=CHCH_2MgCl$ / THF, CuI, reflux for 4 h, then NH_4Cl / H_2O at 0 °C; c) BH_3-THF, rt for 3h, then H_2O, NaOH, H_2O_2 at 0 °C; d) i. TsCl, Py / DCM at 0 °C for 4 h, then at 10 °C for 12h, ii. R_2NH / EtOH reflux for 3h; e) Tf_2O, ii,6-lutidine / DCM at -10 °C for i h, ii. R_2NH / THF, rt for i h.



8 X: H or CH_3 **9** X: H or CH_3

Fig. (1).

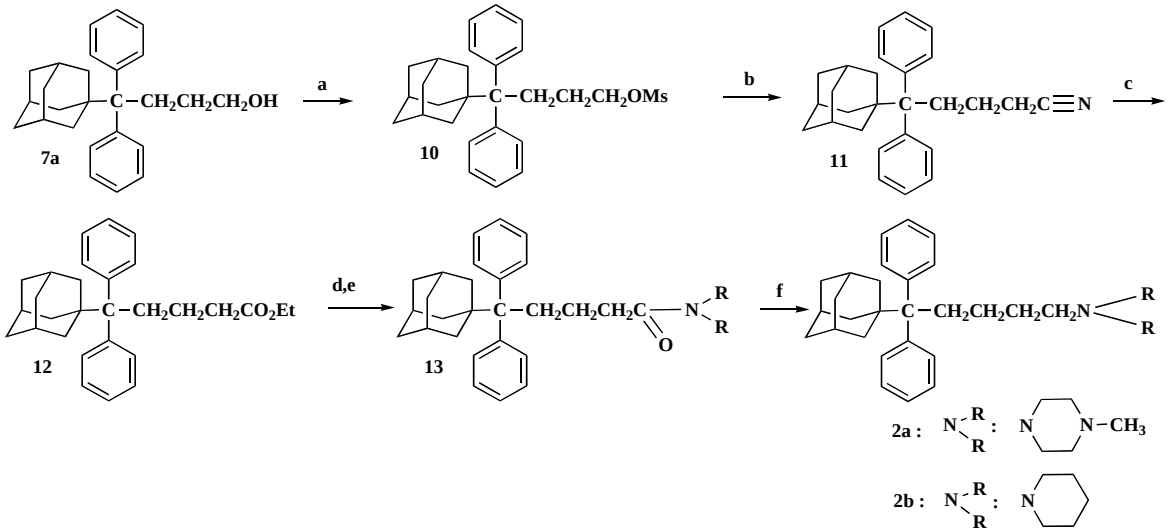
CHEMISTRY

For the preparation of the butylamines **1**, the appropriate *α*,*α*-diaryl-1-adamantylmethanol **4** was used as starting material, which was prepared by addition of the corresponding arylmagnesiumbromide to ethyl 1-adamantanecarboxylate. Indicativelly, *α*-phenyl-*α*-(*p*-tolyl)-1-adamantylmethanol (**4**) (X=CH_3, X′=H) was synthesized from *p*-tolylmagnesium bromide and 1-adamantylphenyl ketone.

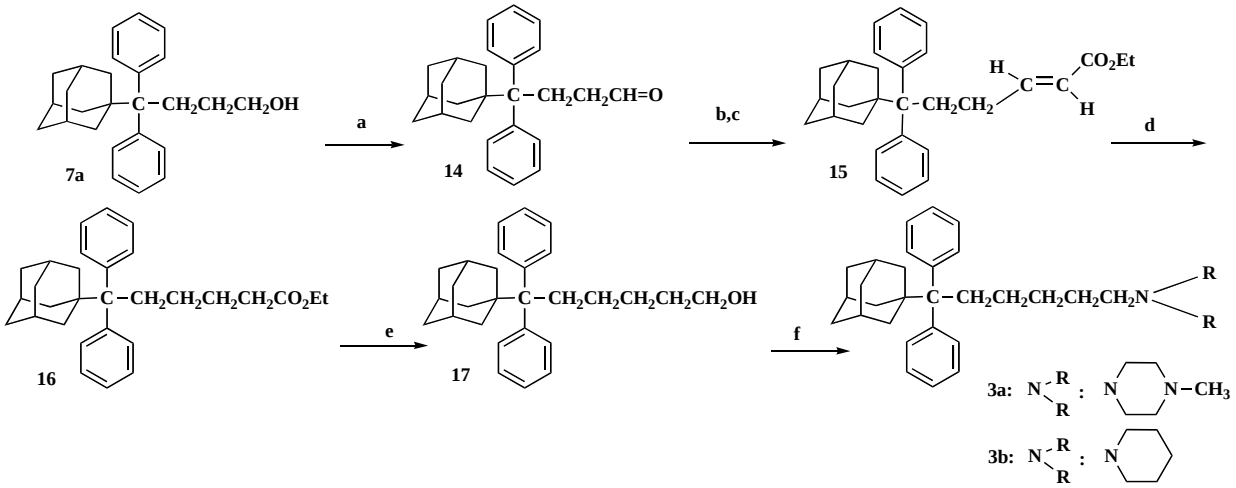
Carbinols **4** were treated with a mixture of thionyl chloride/acetyl chloride to form the corresponding chlorides **5**, which led to the 1-butene analogue **6**, in the presence of allylmagnesium chloride and a catalytic amount of copper (I) iodide. The latter reaction, which proceeds through a radical mechanism, gave the desired olefins **6** (X=X′=CH_3, X=X′=CH_3O, X=X′=F) without any by-product formation. On the contrary, in the case of olefin **6** (X=X′=H and X=CH_3, X′=H), where at least one of the benzene rings was unsubstituted, the reaction led to the formation of 1-(*p*-allylbenzhydryl)adamantanes (**8**) as by-product (Fig. **1**).

It seems that, apart from the main allylic product, *p*-allylation also takes place, via a combination of the allylic and benzhydrylic radical. The ratio of formation of these by-products was approximately 17-20%, according to NMR spectra analysis.

Olefins **6** were purified and then converted to 1-butanols **7** by hydroboration. Conversely, olefins **6** (X=X′=H and X=CH_3, X′=H) were used as mixtures with isomers **8**. The desired corresponding butanols **7** were separated from the



Scheme 2. Reagents and conditions: a) MsCl/Py, DCM anhydrous, rt for 12h; b) NaCN/DMSO at 60 °C for 12h; c) gas HCl/EtOH, reflux for 2h and then a few water drops, reflux for 1h; d) NaOH/EtOH-H_2O, reflux for 2h and then HCl (10%) at 0 °C; e) $SOCl_2$ reflux for 1h and then R_2NH / THF reflux for 8h; f) $LiAlH_4$/THF reflux for 3.5h and then H_2O/NaOH at 0 °C.



Scheme 3. Reagents and conditions: a) PCC, DCM anhydrous, rt for 2h; b) triethyl phosphonoacetate/NaH in THF at 0 °C for 30min; c) i. aldehyde **14** in THF at 0 °C for 30min, ii NH_4Cl/H_2O at 0 °C; d) H_2/Pd-C for 16h; e) $LiAlH_4$/THF, rt for 1h and then H_2O/NaOH at 0 °C; f) i. TsCl/Py, rt for 1h, ii. R_2NH/EtOH reflux for 5h.

benzenepropanols **9**, which were formed by the hydroboration of by-products **8** (Fig. **1**).

Finally, alcohols **7** were converted to butylamines **1** via the intermediate tosylate or trifluoromethanesulfonate. It must be noted that the conversion to trifluoromethanesulfonates upon addition of the requisite secondary amines, an S_N2 substitution pathway, was followed by an E2 elimination. This elimination led to mixtures of the expected amines **1** and olefins **6**, which were purified by chromatography to give the final products **1**.

The synthesis of the pentylamine analogs **2** was accomplished by the reaction sequence shown in Scheme **2**. Butanol **7a** was mesylated to form mesylate **10**, which was converted to nitrile **11** by adding sodium cyanide. Alcoholysis of cyanide **11** with an ethanolic solution of hydrogen chloride gave ethylester **12**, which was saponified to the intermediate carboxylic acid. This was transformed to the corresponding chloride, which coupled with 1-methylpiperazine and piperidine gave the respective carboxamides **13**. Reduction of these amides with $LiAlH_4$ led to the desired pentylamines **2a** and **2b**.

For the preparation of the hexylamines **3**, butanol **7a** was oxidized to butanal **14** with pyridinium chlorochromate. Treatment of aldehyde **14** with triethyl phosphonoacetate / sodium hydride at 0 °C led to the Horner-Emmons product **15**. Catalytic hydrogenation of ester **15** in the presence of 10% palladium on charcoal led to the saturated ester **16**. The latter was reduced with $LiAlH_4$ to the respective hexanol **17**, which was converted to hexylamines **3** via the intermediate tosylates.

RESULTS AND DISCUSSION

In vitro anti-proliferative activities of the new compounds on cancer and normal cell lines are shown in Tables **1a**, **1b** and **1c**.

Table 1a. Summary results from the *in vitro* screening. *For each experimental agent: LC_{50} is the concentration of drug resulting in 50% lethality (50% reduction in measured protein), TGI the concentration resulting in total growth inhibition, GI_{50} the concentration resulting in growth inhibition of 50%. 5-fluorouracil (5FU) was used as reference drug.

		Cancer Cell Lines										Normal Cell Lines		
		Colon		Renal	Prostate		Breast		Ovarian					
Cmpd	Values*	HCT-116	HCT-15	Caki	DU145	PC3	MDA MB231	MCF7	IGROV-1	OVCAR-5	ADR-res NCI	HUVEC	hMSC	NHDF
1a	LC_{50}	8.87	100	9.7	100	45.35	8.7	8.3	8.8	8.6	8.1	8.72	39.22	9.5
	TGI	6.06	8.21	6.91	7.05	7.16	6	5.6	5.9	5,64	5.8	6.00	7.42	6.5
	GI_{50}	3.24	4.41	4.12	4.14	3.8	3.3	3.00	3.00	3.13	3.36	3.29	4.55	3.6
1b	LC_{50}	9.12	20.40	9.29	23.90	71.00	80.3	74	9.94	9.5		8.96	78.63	100
	TGI	6.32	7.02	6.51	7.01	9.70	14.9	16.7	6.68	6.5		6.20	35.1	100
	GI_{50}	3.53	3.94	3.73	3.72	5.20	5.25	5.5	3.41	3.5		3.43	6.84	6.94
1c	LC_{50}	100	81.59	55.55	64.46	70.55	67.12	8.5	100			100	95.81	100
	TGI	9.63	39.95	7.97	9.94	9.56	12.68	35	51			20.24	58.81	54.64
	GI_{50}	4.32	7.65	2.72	7.30	4.44	5.64	7.7	6.22			5.71	21.82	6.83
1d	LC_{50}	100						100				100		
	TGI	100						99.36				100		
	GI_{50}	11.95						22.29				76.76		
1e	LC_{50}	100	8.86		8.29	10.23	8.25	8.72	9.25			8.33	9.88	100
	TGI	7.08	6.05		5.69	7.02	5.84	5.84	6.37			7.13	7.72	7.30
	GI_{50}	3.62	3.23		3.09	3.81	3.44	2.96	3.48			4.14	5.55	3.61
1f	LC_{50}	9.26	8.87	8.50		8.61	8.04	5.51	9.19			10.09	9.55	9.88
	TGI	6.32	6.20	5.98		5.19	5.55	5.90	6.22			6.67	6.95	6.76
	GI_{50}	3.37	3.54	3.46		1.78	3.06	3.33	3.25			3.24	4.35	3.65
1g	LC_{50}	9.05	8.81	8.58		11.11	8.18	8.33	9.32			9.93	9.44	9.40
	TGI	6.16	6.09	6.16		7.58	5.72	5.80	6.32			6.51	7.21	6.21
	GI_{50}	3.26	3.38	3.74		4.01	3.25	3.26	3.32			3.08	4.99	3.02
1h	LC_{50}	9.30	9.96		94.20	89.42		8.76	9.97			9.28		
	TGI	6.39	6.90		30.28	33.91		5.95	6.30			6.54		
	GI_{50}	3.49	3.81		5.81	6.96		3.14	2.63			3.79		
1i	LC_{50}	8.89	8.81	9.13		9.31	8.18	8.71	100			9.66	12.45	10.11
	TGI	6.16	6.02	6.44		6.00	5.58	6.07	7.61			6.62	7.25	7.01
	GI_{50}	3.43	3.23	3.75		2.68	2.97	3.42	4.11			3.58	4.45	3.91
1j	LC_{50}	100	81.81	9.17	100	75.80	44.70	9.10	100	10.10		8.79	91.14	76.82
	TGI	6.56	11.89	6.24	7.09	9.10	8.00	6.30	22.91	6.80		6.06	47.47	8.85
	GI_{50}	2.67	5.15	3.30	3.76	4.70	4.55	3.50	6.20	3.60		3.33	8.44	4.59
1k	LC_{50}	8.37	9.29		22.25	11.83		9.00	9.06			9.20		
	TGI	5.90	6.43		7.63	7.94		6.12	5.96			6.12		
	GI_{50}	3.42	3.58		4.24	4.08		3.22	2.92			3.04		
5FU	LC_{50}	100	100	100	100	100	100	100	100	100	100	100	100	100
	TGI	100	100	100	100	100	100	100	100	100	100	100	55.00	100
	GI_{50}	9.10	9.60	100	43.77	94.40	59.00	4.20	15.21	83.00	7.60	17.70	8.44	6.90

Table 1b. Summary results from the *in vitro* screening. *For each experimental agent: *LC_{50} is the concentration of drug resulting in 50% lethality (50% reduction in measured protein), TGI the concentration resulting in total growth inhibition, GI_{50} the concentration resulting in growth inhibition of 50%. 5-fluorouracil (5FU) and dacarbazine (DIC) were used as reference drug.

		CNS		Non small lung	Small Lung	Leukemia	Pancreas	Liver	Melanoma		primary melanoma
Cmpd	**Values***	**SF268**	**U251**	**NCI-H460**	**DMS 114**	**HL-60 (TB)**	**BX-PC3**	**SKHep1**	**LOX-IMVI**	**SK-MEL-28**	**CCS WD6**
1a	**LC_{50}**	9.2	8.07	9.09	9.94	100	9.08	8.53	8.16	8.28	8.56
	TGI	6.36	5.52	6.26	6.68	9.04	6.24	5.78	5.81	5.79	5.88
	GI_{50}	3.53	2.98	3.44	3.42	5.07	3.41	3.03	3.46	3.29	3.2
1b	**LC_{50}**	86.48	8.15	100	100	73.26	67.3	72.14	8.88	9.05	8.77
	TGI	42.78	5.81	7.96	7.22	7.11	7.79	8.68	6.33	6.37	6.10
	GI_{50}	8.19	3.46	4.13	4.29	3.76	4.02	4.82	3.77	3.68	3.43
1c	**LC_{50}**	93.51		100	94.77	100	100	71.61	62.16	79.17	8.44
	TGI	55.27		46.6	7.18	100	7.77	24.08	13.70	36.05	5.41
	GI_{50}	17.03		6.06	3.2	6.46	3.29	5.66	5.48	7.23	2.38
1d	**LC_{50}**	100		100				100			
	TGI	100		100				100			
	GI_{50}	100		54.74				23.46			
1e	**LC_{50}**	9.19		9.40	8.89	100	8.91	9.32	62.31	8.24	8.23
	TGI	6.45		6.08	6.04	9.85	6.01	6.63	8.23	5.79	5.41
	GI_{50}	3.72		2.76	3.18	5.32	3.11	3.94	5.09	3.34	2.59
1f	**LC_{50}**	8.55	7.79	10.05	8.84	100	8.83	8.82	7.98	8.14	8.18
	TGI	6.02	4.60	6.84	6.02	100	6.05	5.94	5.06	5.60	5.62
	GI_{50}	3.49	1.42	3.64	3.20	5.96	3.28	3.06	2.14	3.06	3.07
1g	**LC_{50}**	8.69	8.93	9.50	9.04	100	8.85	8.71	8.27	8.05	8.21
	TGI	6.15	6.69	6.53	6.42	9.65	6.09	5.92	5.92	5.52	5.70
	GI_{50}	3.61	4.45	3.56	3.79	4.44	3.33	3.14	3.58	2.99	3.19
1h	**LC_{50}**	100		9.84				77.38			
	TGI	8.45		6.66				23.14			
	GI_{50}	4.76		3.48				6.81			
1i	**LC_{50}**	9.33	8.15	9.92	8.73	100	9.07	8.81	8.42	8.19	8.34
	TGI	6.69	5.58	6.81	5.87	100	6.23	6.03	5.72	5.63	5.80
	GI_{50}	4.06	3.01	3.69	3.01	5.46	3.40	3.25	3.02	3.08	3.27
1j	**LC_{50}**	83.63	7.99	81.14	39.98	52.33	19.69	8.83	8.41	8.19	8.34
	TGI	19.83	5.55	8.38	6.08	7.42	6.86	6.10	6.05	5.77	5.67
	GI_{50}	6.57	3.12	4.34	1.59	3.22	3.54	3.37	3.69	3.35	3.00
1k	**LC_{50}**	8.89		9.25			9.29	8.89			
	TGI	6.30		6.31			6.32	6.35			
	GI_{50}	3.72		3.37			3.35	3.82			
5FU	**LC_{50}**	100	100	100	100	100	100	100	100	100	
	TGI	100	100	100	100	100	100	100	100	100	
	GI_{50}	91.56	83.90	5.01	100	100	68.91	9.95	8.38	55.49	
DIC	**LC_{50}**								100		100
	TGI								100		87.33
	GI_{50}								7.40		4.47

Table 1c. Summary results from the *in vitro* screening. *For each experimental agent: * LC_{50} is the concentration of drug resulting in 50% lethality (50% reduction in measured protein), TGI the concentration resulting in total growth inhibition, GI_{50} the concentration resulting in growth inhibition of 50%. 5-fluorouracil (5FU) was used as reference drug.

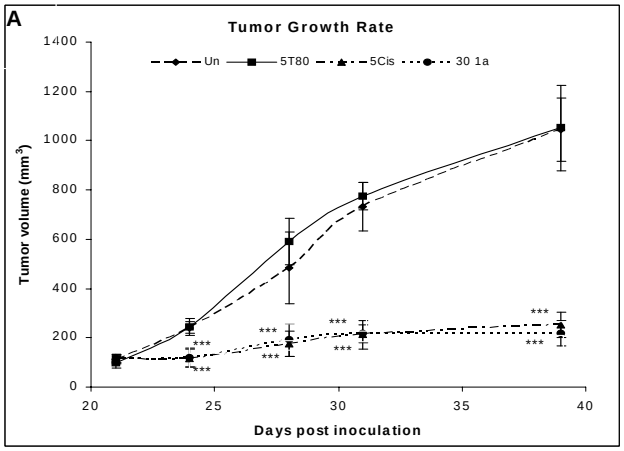
		Colon	Prostate		Leukemia	Breast	Ovarian	Liver
Cmpd	**Values***	**HCT-15**	**DU145**	**PC3**	**HL-60 (TB)**	**MCF7**	**IGROV-1**	**SKHep1**
2a	**LC_{50}**	10.61	9.38	10.39	100	8.44	9.56	9.71
	TGI	7.34	7.03	7.33	7.73	5.71	5.96	6.68
	GI_{50}	4.08	4.63	3.77	4.78	2.98	2.40	3.65
2b	**LC_{50}**	100	24.70	14.62	100	78.65	95.10	71.30
	TGI	78.84	18.02	10.33	9.87	49.50	54.43	16.39
	GI_{50}	8.49	11.31	5.93	6.10	20.50	13.74	5.85
3a	**LC_{50}**	100	13.36	12.88		9.72	10.17	8.61
	TGI	8.93	9.03	8.47		6.60	6.93	6.07
	GI_{50}	4.79	4.69	4.06		3.48	3.71	3.54
3b	**LC_{50}**	100	19.57	18.32		9.88	13.70	8.46
	TGI	8.99	8.41	7.70		6.90	9.67	5.85
	GI_{50}	4.49	5.68	5.57		3.92	5.60	3.24
5FU	**LC_{50}**	100	100	100	100	100	100	100
	TGI	100	100	100	100	100	100	100
	GI_{50}	9.60	43.77	94.40	100	4.20	15.21	9.95

Table 2. Affinities of the adamantane derivatives 1 for the σ1, σ2-receptors and for the site 2 of Na^+ channels, measured by displacement of [^{3}H](+)pentazocine, [^{3}H]1,3-di-*o*-tolylguanidine and [^{3}H]batrachotoxin, respectively.

Cmpd.	σ1 (IC_{50}, nM)	σ2 (IC_{50}, nM)	σ2 / σ1	Sodium Channels (IC_{50}, μM)
1a	15	60	4	0.8
1c	15	4.4	0.3	0.2
1d	96	13	0.14	0.5
1e	22	270	12	0.4
1j	16	480	30	0.3
1k	38	790	21	0.4

Affinities of derivatives **1** for both σ1, σ2 receptors and the site 2 of Na^+ channels are summarized in Table **2**. Moreover, an *in vivo* xenograft screening study using the ovarian cancer cell line (IGROV-1), was conducted for compound **1a** (Fig. **2**).

It is clear, from Table **2**, that analogs 1 exhibit significant σ1 selectivity in the order: **1j ≥ 1k > 1e ≥ 1a**. In contrast, derivatives **1c** and **1d** exhibited lower affinity for σ1 vs σ2 receptors. All compounds showed similar affinities (micromolar to sub-micromolar) for the site 2 of the Na^+ channels. According to the data presented in Table **1**, **1a**, **1k** and **1e**, as well as the phenyl(s) substituted derivatives **1f**, **1g**, **1h** and **1i**, the pentylamines **2a** and **2b** and the hexylamines **3a** and **3b**, have similar anti-proliferative activities in all the cancer cell lines. The rest of these derivatives show anti-proliferative activities in the order: **1j > 1c > 1d**, the last being quasi-inactive. According to the classic data and conceptions [8,9,13,14], concerning the synthesis of selective σ2 agonists [8,9] and mixed σ1 antagonists / σ2 agonists [14], in order to obtain anticancer efficacy [8,9,14], it could be speculated that **1e, 1a** and the derivatives, **1k** and **1j** might behave as mixed σ1 antagonists and weak σ2 agonists.



B	Post mortem weight	
	Average weight ±STDV(mg)	% reduction
untreated	970±66.7	
5T80	990±29.7	
2.5 Cis	280±61.2	69.76 ***
30 1a	270±56.1	73.27 ***

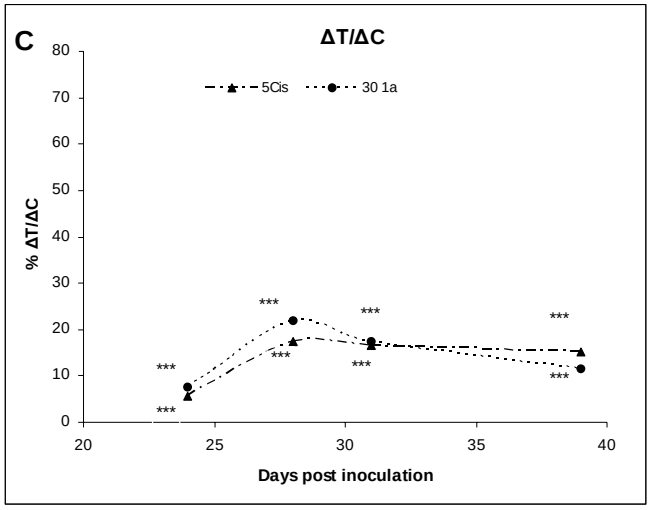


Fig. (2). Growth of IGROV-1 (Ovarian cancer) tumors in SCID mice treated with Cisplatin (reference drug for ovarian cancer) and compound **1a**. (**A**): average tumor size (in mm^3) of each mouse group (8 mice per group that is 16 tumors per group) as a function of time (in Days); error bars represent Standard Deviation; and, (**C**), %ΔT/ΔC as a function of time (in Days) for IGROV-1 xenografts. UT represents untreated animals receiving saline; 5T80 animals treated with 5%Tween80; 2.5 CIS, animals treated with 2.5mg/kg of Cisplatin twice per week and 30 **1a**, animals treated with 30mg/kg of compound **1a** for 5 consecutive days. Statistical evaluation was assessed using one way Anova followed by LSD post hoc test (cisplatin treated animals were compared to untreated animals, whereas 1a-treated animals were compared to their respective controls 5T80 treated animals). Time points with significance, $p \leq 0.05$ are indicated by an asterisk (*), $p \leq 0.001$ by three asterisks (***). Table **B** shows mean weight of tumors extracted upon completion of the experiment and percentage of reduction compared to control groups. Statistical evaluation was assessed using one way Anova followed by LSD post hoc test. Values with significance, $p \leq 0.05$ are indicated by an asterisk (*), $p \leq 0.001$ by three asterisks (***).

In agreement with the σ1 affinities of the new derivatives and the degree of expression of the σ1 receptors in the cancer cells [3,11-13,24] all these ligands (except **1d**) exhibited significant to high cytotoxic activity on all the studied cancer cell lines.

Considering the *in vitro* results of anti-proliferative activity of the new derivatives on cancer cell lines (colon, renal, prostate, breast, ovarian, central nervous system, lung, leukemia, pancreas, melanoma) and on normal cell lines (HUVEC: Human Umbilical Vein Endothelial Cells, hMSC: Human Mesenchymal Stem Cells, NHDF: Normal Human Dermal Fibroblasts) (Table **1a**,**b**,**c**), it appears that **1a** exhibited some selective action against ovarian cancer cells, given that the cytotoxic effect of **1a** on the HUVEC cells could, *in vivo*, also serves as an antiangiogenic factor against the tumors. Compound **1a** was further investigated in a xenograft study (ovarian cancer cell line IGROV-1), which was performed on mice with severe combined immune deficiency (SCID) (Fig. **2**).

Compound **1a** exhibited the same activity, compared to the reference drug cisplatin (Fig. **2**). However, serious central and peripheral painful neuropathy, usually not reversible, is developed in most of the patients treated with therapeutical doses of cisplatin [27-29], compromising the quality of life of cancer patients. In contrast and in good agreement with recent experimental results, concerning the antagonism of neuropathic pain by σ1 antagonists [3,30-34] or voltage gated sodium channels (VGSC) blockers [35-37], a putative analgesic activity of **1a** against the persistent neuropathic pain could be anticipated by the effect obtained (Fig. **3**) in

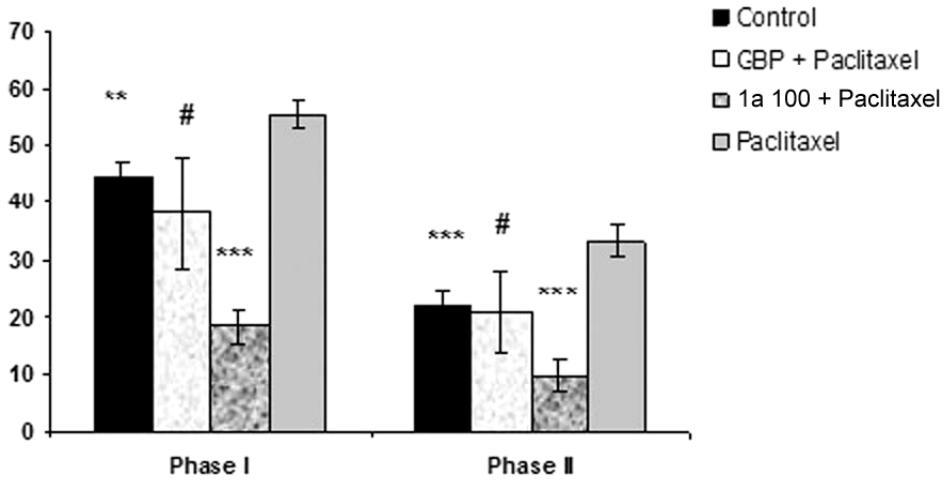


Fig. (3). Effects of orally administered (po) **1a** at the dose of 100mg/kg, on Paclitaxel treated mice in the Formalin test, compared to the reference drug Gabapentin (GBP) 100mgkg ip, (GBP was administered ip since po administration of the compound exerts no analgesic effect in the formalin test, data not shown). One way Anova followed by LSD post hoc test confirmed the expected hyperalgia of Paclitaxel treated animals compared to the Vehicle treated group in both time intervals examined (**p<0.01 and ***p<0.001 respectively). GBP administration in Paclitaxel pretreated animals was found to exert a mild analgesic effect in both time intervals, as indicated by their lower licking, of the administered paw, times compared to Paclitaxel treated animals (#p<0.1 in both intervals). Administration of **1a** exerted a stronger analgesic effect in Paclitaxel treated animals: **1a** Paclitaxel treated animals displayed lower licking times compared to Paclitaxel treated animals both at 0-5min (***p<0.001) and 35-40min (***p<0.001) after formalin injection (see also Experimental section).

the appropriate (formalin) test [38-40], on mice with central and peripheral neuronal sensitization, induced by administration of paclitaxel [41], two weeks before the formalin test [41,42]. In our knowledge for the first time, evidence is given that an *in vivo* putative anticancer activity, obtained by a mixed σ1/σ2 ligand with σ1 preferential affinity, could be associated with an analgesic activity against the neuropathic pain induced by the main anticancer drugs (taxanes, platines).

Finally, in spite of the absence of functional tests allowing the study of the intrinsic activity of the new sigma ligands and also of a clear hypothesis concerning their cytotoxicity against the cancer cells, the recent developments on the role of sigma receptors of the MAM in the modulation of apoptosis [3,6] and of the cell cycle [19] could be considered as a serious basic hypothesis concerning the antiproliferative activity of **1a**.

CONCLUSION

In this work, the design and synthesis of 1-admantyldiarylalkanamine **1**, **2** and **3** were described. The scaffold of the above compounds, which includes two aromatic rings and a hydrophobic adamantane moiety linked to an amine nitrogen atom, is essential for sigma (σ) receptor affinity. The σ1, σ2 receptors and sodium channels binding affinity of derivatives **1**, as well as the in vitro antiproliferative activity of compounds **1**, **2** and **3** were investigated. Compound **1a** was further tested on a xenograft study (ovarian cancer cell line IGROV-1) and its anticancer activity was associated with an anagelsic potency against neuropathic pain.

Xenograft studies are currently underway in order to further investigate the activity of these compounds and especially, in relation to their significant affinity for Na^+ channels, their effects on cancer metastasis and neuropathic pain.

EXPERIMENTAL SECTION

Binding Studies

Binding studies were carried out by CEREP (France) with the σ1 binding assay performed according to Ganapathy *et al*. [43], the σ2 binding assay according to Bowen et al. [44], the sodium channel (site 2) assay according to Brown [45].

Cell Cultures and Cell Lines

All human cancer cell lines were obtained from the National Cancer Institute, NIH (Bethesda, MD, USA) with the exception of BX-PC3 that were obtained from ATCC, the hMSCs, NHF and HUVECs that were purchased from Lonza. All cell lines were adapted to propagate in RPMI 1640 medium supplemented with 5% heat-inactivated fetal calf serum, 2 mM L-glutamine and antibiotics. The cultures were grown in a humidified 37°C-incubator with 5% CO_2 atmosphere.

In Vitro Cytotoxic Activity

Cell viability was assessed at the beginning of each experiment by the trypan blue dye exclusion method, and was always greater than 95%. Cells were seeded into 96-well microtiter plates in 100 μL of medium at a the corresponding density (3500-30000 cells per well) and subsequently, the plates were incubated at standard conditions for 24 h to allow the cells to resume exponential growth prior to addition of the agents to be tested. Then in order to measure the cell population, cells in one plate were fixed *in situ* with TCA followed by SRB staining, as described elsewhere [46,47]. To determine the activity, each compound was dissolved in DMSO and then was added at 10-fold dilutions (from 100 to 0.01 μM) and incubation continued for an additional period of 48 h. The assay was terminated by addition of cold TCA followed by SRB staining and absorbance measurement at

540 nm, in an DAS plate reader, to determine the GI_{50}, that is, the concentration required in the cell culture to inhibit cell growth by 50%, TGI, the concentration that is required to completely inhibit cell growth and the LC_{50}, the concentration that is needed in culture to kill 50% of the cellular population as described [42, 43].

In vivo Antitumor Activity

SCID (NOD.CB17 Prkdcscid) mice were purchased from Jackson Laboratories/Charles River Laboratories (L'Arbresle, France). The mouse colony was maintained under restricted flora conditions in a pathogen-free environment in type IIL-cages. Female mice, 7–9 weeks old, were injected subcutaneously according to the British practice of bilateral trocar implants at the axillary region. Each inoculum contained 10^6 cells exponentially growing at the time of harvesting. The mice were subsequently randomly divided into groups of 10 animals per group. Treatments started when the average tumor volume had reached about 100 mm^3. Tumor volume was calculated as described elsewhwere [48]. All administrations were intraperitoneal. Treated animals received a single injection daily for 5 days per week throughout the experiments. Tumor volume was measured with a calliper twice per week. In addition to tumor volume, we calculated the parameter, $\%\Delta T/\Delta C$, where $\Delta T = T - Do$ and $\Delta C = C - Do$ (Do is the average tumor volume at the beginning of the treatment; T and C are the volumes of treated and untreated tumors, respectively, at a specified day). Concurrently, we scored the number of tumor-free animals, number of drug-related deaths, and average number of days required to reach a defined tumor volume. Optimal $\Delta T/\Delta C$ value was used as a measure of drug activity. Losses of weight, neurological disorders and behavioral and dietary changes were also recorded as indicators of toxicity (side effects). The experiment was terminated when tumor size in untreated animals reached a volume of about 10-11% of animals' weight.

Statistical Analysis

Significant difference in tumor volume was determined by one way Anova followed by LSD post hoc tests using the SPSS for Windows (release 11.0.0, SPSS Inc., USA) software package. A difference was considered significant if $p < 0.05$.

Formalin Test

CD1 male mice weighing 34 to 40g were used. They were kept in a room maintained at 21-22ºC with free access to standard laboratory diet and tap water. Paclitaxel (Brystol Myers Squibb Company) was diluted in saline and administered at one ip injection (6mg/kg) on day 0, as adapted from Matsumoto *et al*. [41]. On day 14, 1hr after oral administration (po) of the compound **1a** (100mg/kg) the formalin test, as a tonic and persistent pain model of nociception, was performed. Injection of formalin into the hind paw is followed by two phases of behavior [42]. The first phase consists of intense licking and biting of the injected paw for the first 5 min followed by a period of little activity. The second phase spans from 15 to 40 min after the formalin injection and involves periods of licking and biting of the injected paw. The first phase is thought to be a model of acute chemical pain, whereas the second phase reflects a state of central sensitization driven by the presumed first phase [38]. The amount of time spent licking and biting the injected paw and leg was recorded in 5-min intervals for 0-5 and 35-40 min after the formalin injection.

MATERIALS AND METHODS

Melting points were determined using a Büchi capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 833 spectrometer. ^1H, ^{13}C NMR spectra were recorded on a Bruker MSL 400 spectrometer using $CDCl_3$ as solvent and TMS as internal standard. Carbon multiplicities were established by DEPT experiments. 2D NMR experiments (HMQC, COSY and NOESY) were performed for the elucidation of the structures of the new compounds. Microanalyses were carried out by the Service Central de Microanalyse (CNRS) France, and the results obtained had a maximum deviation of ±0.4% from the theoretical value.

α,α-Diphenyl-1-tricyclo[3.3.1.1.^{3,7}]decanemethanol (4a)

Carbinol **4a** was prepared by addition of phenylmagnesium bromide to ethyl 1-adamantanecarboxylate [49]. Yield 89%. Mp 127-128 ^oC (ether).

α,α-Bis(4-methylphenyl)-1-tricyclo[3.3.1.1.^{3,7}]decanemethanol (4f)

Carbinol **4f** was synthesized by adding *p*-tolylmagnesium bromide to ethyl 1-adamantanecarboxylate in a similar way as for carbinol **4a**. Yield 70%. Mp 144-146 ^oC (ether - *n*-pentane); IR (Nujol) v (OH) 3608cm-1; ^{1}H-NMR(400MHz, $CDCl_3$) δ(ppm): 1.52-1.56(m, 6H, 2, 8, 9-H), 1.78(br.s, 6H, 4, 6, 10-H), 1.91(br.s, 3H, 3, 5, 7-H), 2.12(s, 1H, OH), 2.23(s, 6H, CH3), 6.98-7.00(d, 4H, AA`BB`, J_{AB}~8.5 Hz, $J_{AA`}=J_{BB`}=0$ Hz, 3, 5 -Har), 7.36-7.38(d, 4H, AA`BB`, J_{AB}~8.5 Hz, $J_{AA`}=J_{BB`}=0$ Hz, 2, 6-Har); ^{13}C-NMR(100MHz, $CDCl_3$) δ(ppm): 20.88(CH_3), 28.79(3, 5, 7-C), 36.92(2, 8, 9-C), 37.36(4, 6, 10-C), 40.99(1-C), 81.97(*α*-C), 127.79(3, 5-Car), 128.42(2, 6-Car), 135.79(1-Car), 142.58(4-Car); Anal. Calcd for $C_{25}H_{30}O$, C: 86.65; H: 8.73. Found: C: 86.80; H: 8.54.

α,α-Bis(4-methoxyphenyl)-1-tricyclo[3.3.1.1.^{3,7}]decanemethanol (4g)

Carbinol **4g** was synthesized by adding p-anisylmagnesium bromide to ethyl 1-adamantanecarboxylate in a similar way as for carbinol **4a**. *p*-Anisylmagnesium bromide was prepared from *p*-bromoanisole and magnesium turnings in the presence of equimolar volume of THF and anhydrous benzene. Yield 60%. Mp : 139-140 ^oC (ether); IR (Nujol) v (OH) 3481cm^{-1}; ^{1}H-NMR(400MHz, $CDCl_3$) *δ* 1.56-1.64(m, 6H, 2, 8, 9-H), 1.81-1.82(m, 6H, 4, 6, 10-H), 1.97(br.s, 3H, 3, 5, 7-H), 2.17(s, 1H, OH), 3.76(s, 3H, OCH_3), 6.76-6.79(~d, 4H, AA`BB`, J_{AB}~9 Hz, $J_{AA`}=J_{BB`}=0$ Hz, 3, 5-Har), 7.44-7.46(~d, 4H, AA`BB`, J_{AB}~9 Hz, $J_{AA`}=J_{BB`}=0$ Hz, 2, 6-Har); ^{13}C-NMR(100MHz, $CDCl_3$) *δ* 28.8(3, 5, 7-C), 36.9(2, 8, 9-C), 37.4(4, 6, 10-C), 41.1(1-C), 55.09(CH_3O), 81.7(*α*–C), 112.3(3, 5-Car), 129.7(2, 6-Car), 137.8(1-Car), 157.8(4-Car); Anal. Calcd for $C_{25}H_{30}O_3$, C: 79.33; H: 7.99. Found C: 79.45; H: 8.02.

α,α-Bis(4-fluorophenyl)-1-tricyclo[3.3.1.1.^{3,7}]decanemethanol (4h)

Carbinol **4h** was synthesized by adding *p*-fluorophenylmagnesium bromide to ethyl 1-adamantanecarboxylate in a similar way as for carbinol **4a**. Yield 45%; Mp 117-119 ^{o}C (ether- n-pentane); IR (Nujol) v (OH) 3610cm^{-1}; 1H-NMR(400MHz, $CDCl_3$) δ 1.52-1.62(m, 6H, 2, 8, 9-H), 1.76(br.s, 6H, 4, 6, 10-H), 1.94(br.s, 3H, 3, 5-H), 2.21(s, 1H, OH), 6.86-6.91(t, 4H, $J_{2ar,3ar} \sim J_{3ar,F}$= 8.7 Hz, $J_{3ar,5ar}$=0 Hz, 3, 5-Har), 7.42-7.46(q, 4H, $J_{2ar,3ar}$=8.7 Hz, $J_{2ar,F}$=5.5 Hz, $J_{2ar,6ar}$=0 Hz, 2, 6 -Har); ^{13}C-NMR(100MHz, $CDCl_3$) δ 28.7(3, 5, 7-C), 36.8(2, 8, 9-C), 37.3(4, 6, 10-C), 41.0(1-C), 81.72(α-C), 113.8, 114.0(3, 5-Car), 130.2, 130.3(2, 6-Car), 140.9(1-Car), 162.5(4-Car); Anal. Calcd for $C_{23}H_{24}F_2O$, C: 77.94; H: 6.83. Found C: 78.05; H: 6.62.

α-(4-Methylphenyl)-α-phenyl-1-tricyclo[3.3.1.1.^{3,7}]decanemethanol (4i)

To a stirred solution of *p*-tolylmagnesium bromide, which was prepared from magnesium turnings (0.8 g, 0.032 gr-at) and 4-bromotoluene (6 g, 0.035 mol) in anhydrous diethyl ether (50 ml) was added dropwise a solution of 1-adamantyl phenyl ketone (3.4 g, 0.014 mol) in anhydrous diethyl ether (50 ml), under an argon atmosphere. The mixture was heated to mild reflux for 1 h, then quenched by adding water and a solution of HCl 10% in an ice bath. The organic layer was separated and extracted with diethyl ether. The combined organics were washed with water, saturated solution of Na_2CO_3 (10%), dried over Na_2SO_4 and concentrated jn vacuo. The residue obtained, was crystallized and triturated with *n*-pentane to give 2.8 g of a solid product (Yield 60%). Mp 146-148 ^{o}C (ether - n-pentane); IR (Nujol) v (OH) 3651cm^{-1}; ^{1}H-NMR(400MHz, $CDCl_3$) δ 1.56-1.64(m, 6H, 2, 8, 9-H), 1.84(br.s, 6H, 4, 6, 10-H), 1.97(br.s, 3H, 3, 5, 7-H), 2.21(s, 1H, OH), 2.28(s, 3H, CH_3), 7.04-7.06(d, 2H, AA`BB`, $J_{AB} = J_{A`B`}$= 8 Hz, $J_{AA`}=J_{BB`}$=0 Hz, 3, 5-Har), 7.14-7.19(q, 1H, 4`- Har), 7.21-7.25(~t, 2H, 2`,6`-Har), 7.43-7.45(d, 2H, AA`BB`, $J_{AB} = J_{A`B`}$= 8 Hz, $J_{AA`}=J_{BB`}$=0 Hz, 2, 6-Har), 7.52-7.54(~d, 2H, 3`,5`- Har); $^{13}$C-NMR(100MHz, $CDCl_3$) $\delta$ 20.9($CH_3$), 28.8(3, 5, 7-C), 36.9(2, 8, 9-C), 37.4(4, 6, 10-C), 41.0(1-C), 82.1($\alpha$-C), 126.3(4`-Car), 127.0(2`, 6`-Car), 127.9(3, 5-Car), 128.5(3`, 5`-Car), 128.5(2, 6-Car), 135.9(1-Car), 142.5(1`-Car), 145.5(4-Car); Anal. Calcd for $C_{24}H_{28}O$, C: 86.70; H: 8.49. Found C: 86.35; H: 8.42.

α,α-Diphenyl-1-tricyclo[3.3.1.1.^{3,7}]decylmethyl chloride (5a) [49]

A mixture of carbinol **4a** (5 g, 0.016 mol), thionyl chloride (30 ml) and acetyl chloride (20 ml) was heated to mild reflux for 30 min. The excess of thionyl chloride and acetyl chloride was evaporated under vacuum and the last traces were removed azeotropically with anhydrous benzene. The solid residue was recrystallized from ether, n-pentane to give 3.9 g of the product. (Yield 72%). Mp 150-152 ^{o}C.

α,α-Bis(4-methylphenyl)-1-tricyclo[3.3.1.1.^{3,7}]decylmethyl chloride (5f)

Chloride **5f** was synthesized in a similar way to chloride **5a**. Yield 74%; Mp 103-105 ^{o}C (ether - *n*-pentane).

α,α-Bis(4-methoxyphenyl)-1-tricyclo[3.3.1.1.^{3,7}]decylmethyl chloride (5g)

Chloride **5g** was synthesized in a similar way to chloride **5a**. Yield 45%; Mp 89-90 ^{o}C (ether - *n*-pentane).

α,α-Bis(4-fluorophenyl)-1-tricyclo[3.3.1.1.^{3,7}]decylmethyl chloride (5h)

Chloride **5h** was synthesized in a similar way to chloride **5a**. Yield 70%; Mp 146-148 ^{o}C (ether - *n*-pentane).

α-(4-Methylphenyl)-α-phenyl-1-tricyclo[3.3.1.1.^{3,7}]decylmethyl chloride (5i)

Chloride **5i** was synthesized in a similar way to chloride **5a**. Yield 90% (viscous product). The product was used to the next step as such.

4,4-Diphenyl-4-(1-tricyclo[3.3.1.1.^{3,7}]decyl)-1-butene (6a)

To a stirred solution of allylmagnesium chloride (2 M) in THF (14 ml, 27 mmol), was added dropwise a solution of chloride **5a** (3 g, 9 mmol) in anhydrous THF (30 ml) in the presence of catalytic amount of copper (I) iodide, under an argon atmosphere. The reaction mixture was heated to reflux for 4 h and then quenched by adding a saturated solution of NH_4Cl at 0 ^{o}C. The mixture was filtered off and the filtrate was evaporated to remove the solvent. Water was added into the residue and the mixture was extracted with ether. The combined organics were washed with water, dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography, using as eluent cyclohexane to give 2.84 g of an oily product (yield 92%). ^{1}H-NMR spectrum analysis proved that there was a mixture of butene **6a** and compound **8a**. The ratio of the two isomers was **6a**:**8a**, 5:1 (~83% of **6a**). The two isomers could not be separated by chromatography and the mixture was submitted to the next step of hydroboration. In order to get a pure sample of butene **6a**, the mixture was frozen at -20 ^{o}C and the crystals formed, were washed with chilled *n*-pentane. Mp 99-101 ^{o}C (*n*-pentane); IR (Nujol) v (C=C) 1632cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.48-1.57(m, 6H, 2, 8, 9-H), 1.77(br.s, 6H, 4, 6, 10-H), 1.89(br.s, 3H, 3, 5, 7-H), 2.92- 2.93(d, 2H, J~7 Hz, γ-H), 4.68-4.78(qd, 2H, α-H), 5.40-5.47(m, 1H, β-H),7.09-7.18(m, 6H, 2, 4, 6-Har), 7.24-7.26(m, 4H, 3, 5-Har); ^{13}C-NMR(100MHz, $CDCl_3$) δ 29.3(3, 5, 7-C), 37.0(2, 8, 9-C), 38.7(4, 6, 10-C), 39.9(1-C), 41.2(γ-C), 58.0(δ-C), 116.1(α-C), 125.3(4-Car), 126.5(2, 6-Car), 131.5(3, 5-Car), 137.2(β-C), 145.4(1-Car); Anal. Calcd for $C_{26}H_{30}$, C: 91.17; H: 8.83. Found C: 91.07; H: 8.90.

4,4-Bis(4-methylphenyl)-4-(1-tricyclo[3.3.1.1.^{3,7}]decyl)-1-butene (6f)

Butene **6f** was prepared from chloride **5f** in a similar way to butene **6a**. It was purified by flash column chromatography, using cyclohexane as eluent. Yield 75%; Mp 104-105 ^{0}C (*n*-pentane); IR (Nujol) ν (C=C) 1630cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.58-1.72(m, 6H, 2, 8, 9-H), 1.83(br.s, 6H, 4, 6, 10-H), 1.97(br.s, 3H, 3, 5, 7-H), 2.33(s, 6H, CH_3), 2.97- 2.99(d, 2H, J~ 7 Hz, γ-H), 4.78-4.90(qd, 2H, α-H), 5.46-5.56(m, 1H, β-H), 7.03-7.05(d, 4H, AA`BB`, J_{AB}~8Hz, $J_{AA`}=J_{BB`}$~0Hz, 3, 5-Har), 7.21-7.24(d, 4H, AA`BB`,

J_{AB}~8Hz, $J_{AA`=}J_{BB`}$~0Hz, 2, 6-Har); ^{13}C-NMR(100MHz, $CDCl_3$) δ 20.8(CH_3), 29.4(3, 5, 7-C), 37.0(2, 8, 9-C), 38.7(4, 6, 10-C), 39.9(1-C), 41.1(γ-C), 57.2(δ -C), 115.9(α-C), 127.2(2, 6-Car), 131.4(3, 5-Car), 134.6(4-Car), 137.5(β-C), 142.3(1-Car); Anal. Calcd for $C_{28}H_{34}$, C: 90.75; H: 9.25. Found C: 90.87; H: 9.17.

4,4-Bis(4-methoxyphenyl)-4-(1-tricyclo[3.3.1.1.^{3,7}]decyl)-1-butene (6g)

Butene **6g** was prepared from chloride **5g** in a similar way to butene **6a**, which was purified by flash column chromatography using as eluent a mixture of ether : cyclohexane, 1:3. Yield 63%. (semisolid); IR (Nujol) v (C=C) 1635cm^{-1}; ^{1}H-NMR(400MHz, $CDCl_3$) δ 1.48-1.62 (m, 6H, 2, 8, 9-H), 1.79(br.s, 6H, 4, 6, 10-H), 1.95(br.s, 3H, 3, 5, 7-H), 2.93-2.95(d, 2H, *J*~ 6.5 Hz, γ-H), 3.79(s, 6H, CH_3O), 4.76-4.87(qd, 2H, α-H), 5.44-5.54(m, 1H, β-H),6.75-6.77(~d, 4H, AA`BB`, J_{AB}~9Hz, $J_{AA`}=J_{BB`}$~0Hz, 3, 5-Har), 7.23-7.25(d, 4H, AA`BB`, J_{AB}~9Hz, $J_{AA`}=J_{BB`}$~0Hz, 2, 6 -Har); ^{13}C-NMR(100MHz, $CDCl_3$) δ 29.30(3, 5, 7-C), 36.97(2, 8, 9-C), 38.68(4, 6, 10-C), 40.04(1-C), 41.23(γ-C), 55.04(CH_3O), 56.61(δ-C), 111.68(3, 5-C), 116.03(α-C), 132.35(2, 6-Car), 137.37(1-Car, β-C), 156.93(4-Car).

4,4-Bis(4-fluorophenyl)-4-(1-tricyclo[3.3.1.1.^{3,7}]decyl)-1-butene (6h)

Butene **6h** was prepared from the chloride **5h** in a similar way to the butene **6a**, which was purified by flash column chromatography using as eluent a mixture of ether : cyclohexane, 1:3. Yield 90%. Mp 116-118 ^{o}C (*n*-pentane); IR (Nujol) *v* (C=C) 1638 cm^{-1}; ^{1}H-NMR(400MHz, $CDCl_3$) δ 1.51-1.60(m, 6H, 2, 8, 9-H), 1.72(br.s, 6H, 4, 6, 10 -H), 1.91(br.s, 3H, 3, 5, 7 -H), 2.87- 2.88(d, 2H, J~ 6.5 Hz, γ-H), 4.72-4.78(m, 2H, α-H), 5.37-5.42(m, 1H, β-H), 6.83-6.87(~t, 4H, $J_{2ar,3ar}$ ~ $J_{3ar,F}$= 8.7 Hz, $J_{3ar,5ar}$=0 Hz, 3, 5 -Har), 7.18-7.21(q, 4H, $J_{2ar,3ar}$=8.7 Hz, $J_{2ar,F}$=5.5 Hz, $J_{2ar,6ar}$=0 Hz, 2, 6-Har); ^{13}C-NMR(100MHz, $CDCl_3$) δ 29.2(3, 5, 7-C), 36.9(2, 8, 9-C), 38.6(4, 6, 10-C), 39.9(1-C), 41.4(γ-C), 57.2(δ-C), 113.2, 113.4(3, 5-Car), 116.9(α-C), 132.7, 132.8(2, 6-Car), 136.5(β-C), 140.7(1-Car), 159.4, 161.9(4-Car); Anal. Calcd for $C_{26}H_{28}F_2$, C: 82.5; H: 7.46. Found C: 82.64; H: 7.45.

4-(4-Methylphenyl)-4-phenyl-4-(1-tricyclo[3.3.1.1.^{3,7}]decyl)-1-butene (6i)

Butene **6i** was prepared from chloride **5i** in a similar way to butene **6a**. Flash column chromatography using as eluent a mixture of ether : cyclohexane, 1:1 gave an oily product (yield 93%), which was found to be a mixture of isomers **6i**:**8i**, 5:1. This mixture was used as such to the next step of hydroboration.

δ,δ-Diphenyl-δ-(1-tricyclo[3.3.1.1.^{3,7}]decane)butanol (7a)

To a stirred solution of a mixture of alkenes **6a**:**8a**, 5:1 (3 g, 8.8 mmol) in anhydrous THF (20 ml) was slowly added a solution of borane 1.0 M in anhydrous THF (9 ml, 9 mmol) under an argon atmosphere at 0 ^{o}C. The reaction mixture was stirred at r.t. for 3 h and then quenched by adding chilled water until no foaming was further formed. A solution of NaOH 10% (4 ml) and H_2O_2 30% (4 ml) was added dropwise into the latter mixture, which was heated to 50-60 ^{o}C for 1 h. The solvent was removed under vacuum and water was added into the residue. The resulting mixture was extracted with ether, the combined organic phases were washed with water, dried over Na_2SO_4 and concentrated in vacuo to give a residue, which was further purified by flash column chromatography, using as eluent a mixture of cyclohexane:ethyl acetate, 4:1 to give 1.1 g of crystalline butanol **9a**. (Yield 41%, calculated from pure starting material); Mp 89-91 ^{o}C (ether); IR (Nujol) v (OH) 3294 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.07-1.18(m, 2H, β-H), 1.50-1.57(m, 7H, 2, 8, 9-H, OH), 1.70(br.s, 6H, 4, 6, 10-H), 1.85(br.s, 3H, 3, 5, 7-H), 2.05-2.09(m, 2H, γ-H), 3.35-3.39(m, 2H, α-H), 7.07-7.15(m, 6H, 2, 4, 6 -Har), 7.24-7.27(m, 4H, 3, 5-Har); ^{13}C-NMR (100MHz, $CDCl_3$) δ 29.2(β-C), 29.3(3, 5, 7-C), 32.0(γ -C), 36.9(2, 8, 9-C), 38.8(4, 6, 10-C), 40.1(1-C), 57.98(δ-C), 63.4(α-C), 125.5(4-Car), 126.5(2, 6-Car), 131.2(3, 5-Car), 144.9(1-Car). Anal. Calcd for $C_{26}H_{32}O$, C: 86.62; H:8.95. Found C: 86.89; H:8.99.

4–[α-(1-Tricyclo[3.3.1.1.^{3,7}]decyl)phenylmethyl]-γ-benzene propanol **8a** (500 mg) was eluted in the next fractions. Mp 71-73 ^{o}C (*n*-pentane); IR (Nujol) v (OH) 3335 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.55-1.64 (complex m, 13H, 2, 4, 6, 8, 9, 10-H, OH), 1.83-1.87(m, 2H, β-H, 1.93(br.s, 3H, 3, 5, 7-H), 2.63-2.67(t, 2H, *J*~7.5-8Hz, γ-H), 3.45(s, 1H, δ-H), 3.63-3.66(t, 2H, *J*~6.5 Hz, α-H), 7.08-7.10(~d, 2H, AA`BB`, $J_{AB}=J_{A`B`}$~8 Hz, $J_{AA`}=J_{BB`}$=0Hz, 2, 6-Har), 7.16-7.23(m, 1H, 4`-Har), 7.25-7.27(m, 2H, 2`, 6`-Har), 7.33-7.35(~d, 2H, AA`BB`, $J_{AB}=J_{A`B`}$~8Hz, $J_{AA`}=J_{BB`}$=0 Hz, 3, 5-Har), 7.40-7.43(m, 2H, 3`, 5`-Har); $^{13}$C-NMR(100MHz, $CDCl_3$) $\delta$ 28.8(3, 5, 7-C), 31.5($\gamma$-C), 34.1($\beta$-C), 36.8(2, 8, 9-C), 41.1(1, 4, 6, 10-C), 62.4($\alpha$-C), 66.0($\delta$-C), 125.9(4`-Car), 127.8(2`, 6`-Car), 127.9(2, 6-Car), 130.0(3, 5, 3`, 5`-Car), 139.3(1`-Car), 139.7(1-Car), 142.3(4-Car).

δ,δ-Bis(4-methylphenyl)-δ-(1-tricyclo[3.3.1.1.^{3,7}]decane) butanol (7f)

Butanol **7f** was prepared in a similar way to butanol **7a** upon hydroboration of allylderivative **6f**. Yield 55%. Mp 62-64 ^{o}C (ether); IR (Nujol) v (OH) 3364 cm^{-1}; ^{1}H-NMR(400MHz, $CDCl_3$) δ 1.10(br.s, 1H, OH), 1.17-1.20(m, 2H, β-H), 1.55-1.62(m, 6H, 2, 8, 9-H), 1.76(br.s, 6H, 4, 6, 10-H), 1.93(br.s, 3H, 3, 5, 7-H), 2.11- 2.14(m, 2H, γ-H), 2.32(s, 6H, CH_3) 3.48-3.51(m, 2H, α-H), 7.02-7.04(~d, 4H, AA`BB`, J_{AB}~8Hz, $J_{AA`}=J_{BB`}$~0Hz, 2, 6-Har), 7.21-7.23(~d, 4H, AA`BB`, J_{AB}~8Hz, $J_{AA`}=J_{BB`}$~0Hz, 3, 5 -Har); ^{13}C-NMR(100MHz, $CDCl_3$) δ 20.81(CH_3), 29.3(β-C), 29.4(3, 5, 7-C), 32.0(γ-C), 37.0(2, 8, 9-C), 38.9(4, 6, 10-C), 40.2(1-C), 57.4(δ-C), 63.7(α-C), 127.3(2, 6-Car), 131.2(3, 5-Car), 134.7(4-Car), 141.9(1-Car). Anal. Calcd for $C_{28}H_{36}O$, C: 86.54; H:9.34. Found C: 86.74; H:9.55.

δ,δ-Bis(4-methoxyphenyl)-δ-(1-tricyclo[3.3.1.1.^{3,7}]decane) butanol (7g)

Butanol **7g** was prepared in a similar way to butanol **7a** upon hydroboration of allylderivative **6g** Yield 55%. Mp 69-71 ^{o}C (ether); IR (Nujol) v (OH) 3350cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.10-1.13(m, 2H, β-H), 1.28(br.s, 1H, OH), 1.50-1.55(m, 6H, 2, 8, 9-H), 1.68(br.s, 6H, 4, 6, 10 -H), 1.86(br.s, 3H, 3, 5, 7-H), 2.02- 2.06(m, 2H, γ-H), 3.41-3.44(t, 2H, *J*~6.4Hz, α-H), 3.73(s, 6H, CH_3O), 6.69-6.71(~d, 4H,

AA`BB`, J_{AB}~8Hz, $J_{AA`}=J_{BB`}$~0Hz, 3, 5-Har), 7.17-7.19(~d, 4H, AA`BB`, J_{AB}~8Hz, $J_{AA`}=J_{BB`}$~0Hz, 2, 6-Har); ^{13}C-NMR(100MHz, $CDCl_3$) δ 29.2(β-C), 29.4(3, 5, 7-C), 32.1(γ-C), 37.0(2, 8, 9-C), 38.8(4, 6, 10-C), 40.3(1-C), 55.1(CH_3O), 56.7(δ-C), 63.7(α-C), 111.8(3, 5-Car), 132.1(2, 6-Car), 137.0(1-Car), 157.0(4-Car). Anal. Calcd for $C_{28}H_{36}O_3$, C: 79.96; H: 8.63. Found C: 80.29; H: 8.64.

δ,δ-Bis(4-fluorophenyl)-δ-(1-tricyclo[3.3.1.1.^{3,7}]decane) butanol (7h)

Butanol **7h** was prepared in a similar way to butanol **7a**. Yield 77%. Mp 59-61 ^{o}C (ether); IR (Nujol) ν (OH) 3335 cm^{-1}; ^{1}H-NMR(400MHz, $CDCl_3$) δ 1.05-1.08(m, 2H, β-H), 1.34-1.56(m, 6H, 2, 8, 9-H), 1.55(br.s, 1H, OH), 1.65(br.s, 6H, 4, 6, 10-H), 1.86(br.s, 3H, 3, 5, 7 -H), 2.03-2.07(m, 2H, γ-H), 3.41-3.45(t, 2H, J~6.5Hz, α-H), 6.81-6.89(m, 4H, 3, 5-Har), 7.17-7.20(m, 4H, 2, 6-Har); ^{13}C-NMR(100MHz, $CDCl_3$) δ 29.1(β-C), 29.3(3, 5, 7-C), 32.2(γ -C), 36.8(2, 8, 9-C), 38.8(4, 6, 10-C), 40.2(1-C), 57.2(δ-C), 63.41(α-C), 113.2, 113.5(3, 5-Car), 132.5(2, 6-Car), 140.4(1-Car), 159.4, 161.9(4-Car). Anal. Calcd for $C_{26}H_{30}F_2O$, C: 78.76; H: 7.63. Found C: 78.70; H: 7.60.

δ-(4-Methylphenyl)-δ-phenyl-δ-(1-tricyclo[3.3.1.1.^{3,7}] decyl)butanol (7i)

Butanol **7i** was synthesized by hydroboration of a mixture of alkenes **6i**:**8i**, which contains 17% of the byproduct. Yield 54% (calculated to the pure starting material). Mp 39-41 ^{o}C (*n*-πεντάνιο). IR (Nujol) ν (OH) 3348 cm^{-1}; 1H-NMR(400MHz, $CDCl_3$) δ 1.11-1.16(m, 2H, β -H), 1.27(br.s, 1H, OH), 1.53-1.56(m, 6H, 2, 8, 9-H), 1.72(br.s, 6H, 4, 6, 10-H), 1.88(br.s, 3H, 3, 5, 7-H), 2.07- 2.12(m, 2H, γ-H), 2.27(s, 3H, CH_3) 3.43-3.46(t, 2H, J~6.5Hz, α-H), 6.97-6.99(~d, 2H, J~8Hz, 3, 5-Har), 7.12-7.20(~m, 5H, 2, 6, 2`, 4`, 6`-Har), 7.28-7.30(~d, 2H, $J$~8.5Hz, 3`, 5`-Har); $^{13}$C-NMR(100MHz, $CDCl_3$) $\delta$ 20.81($CH_3$), 29.3($\beta$-C), 29.4(3, 5, 7-C), 32.0($\gamma$-C), 37.0(2, 8, 9-C), 38.9(4, 6, 10-C), 40.2(1-C), 57.7($\delta$-C), 63.7($\alpha$-C), 125.3(3, 5-Car), 126.6(2, 6 -Car), 127.3(2`, 6`-Car), 131.2, 131.3(3`, 4`, 5`-Car), 134.7(4-Car), 141.8(1-Car), 145.0(1`-Car). Anal. Calcd for $C_{27}H_{34}O$, C: 86.58; H: 9.15. Found C: 86.63; H: 9.13.

4-[4,4–Diphenyl-4-(1-tricyclo[3.3.1.1.^{3,7}]decyl)butyl]-1-methylpiperazine (1a)

(Tosylate method): To a stirred mixture of *p*-toluenesulfonyl chloride (2.51 g, 13.17 mmol) and anhydrous pyridine (6.2 ml) in anhydrous DCM (2.5 ml) was added dropwise a solution of butanol **7a** (2.37 g, 6.58 mmol) in anhydrous DCM (6 ml) at 0 ^{o}C. The reaction mixture was stirred under an argon atmosphere, at 0 ^{o}C for 4 h and then at 10 ^{o}C overnight. The mixture was quenched with a solution of HCl (10%), the organic layer was separated from the aqueous and extracted with DCM. The combined organic phases were washed with water and a solution of Na_2CO_3, dried over Na_2SO_4 and evaporated under vacuum to afford 3.2 g of tosylate (yield ~94%), which was used to the next step without any further purification. To a solution of the tosylate (1.03 g, 2 mmol) in absolute ethanol (10 ml) was added 1-methylpiperazine (4.5 ml) and the reaction mixture was heated to reflux for 3 h. The solvent was then removed under vacuum, water was poured into the residue and the resulting mixture was extracted with ether. The organic layer was thoroughly washed with water, dried over Na_2SO_4 and evaporated to give a residue, which was purified by flash column chromatography, using as eluent a mixture of $CHCl_3$:MeOH, 97:3 to afford 700 mg of liquid product (yield 79%). Total yield from butanol **7a** ~75%. ^{1}H-NMR(400MHz, $CDCl_3$) δ 1.04-1.21(m, 2H, β-H), 1.54-1.62(m, 6H, 2, 8, 9-H), 1.77(br.s, 6H, 4, 6, 10-H), 1.93(br.s, 3H, 3, 5, 7-H), 2.06- 2.10(~t, 2H, J~8Hz, γ-H), 2.17-2.20(~t, 2H, J~7.6Hz, α-H), 2.24(s, 3H, CH_3), 2.20-2.53(very br.s, 8H, 2, 3, 5, 6-Hp), 7.15-7.22(m, 6H, 2, 4, 6-Har), 7.31-7.33(~d, 4H, J~7Hz, 3, 5-Har); ^{13}C-NMR(100MHz, $CDCl_3$) δ 23.0(β-C), 29.3(3, 5, 7-C), 35.58(γ -C), 36.9(2, 8, 9-C), 38.8(4, 6, 10-C), 40.1(1-C), 46.0(CH_3), 53.2(3, 5-Cp), 55.1(2, 6-Cp) 58.2(δ-C), 59.3(α-C), 125.2(4-Car), 126.6(2, 6-Car), 131.2(3, 5-Car), 145.1(1-Car); Dihydrochloride: Mp 263-265 ^{o}C (EtOH-Et_2O); IR (Nujol)ν(OH) 3401 cm^{-1}; Anal. Calcd for $C_{31}H_{44}Cl_2N_2 \cdot H_2O$, C: 69.77; H: 8.69; N: 5.25. Found C: 69.69; H: 8.59; N: 5.17.

4-[4,4–Diphenyl-4-(1-tricyclo[3.3.1.1.^{3,7}]decyl)butyl]-1-ethylpiperazine (1b)

(Trifluoromethanesulfonate method). To a stirred solution of butanol **7a** (361 mg, 1 mmol) in anhydrous DCM (10 ml), was added dropwise 2,6-lutidine (180 mg, 1.7 mmol) and trifluoromethanesulfonic anhydride (470 mg, 1.7 mmol) at -10 ^{o}C. The reaction mixture was stirred at this temperature, under an argon atmosphere for 1 h. Then the solvent was removed under vacuum, without heating and chilled water was poured into the residue. The resulting mixture was extracted with diethyl ether. The combined organic phase was washed with water, dried over Na_2SO_4 and evaporated under vacuum, without heating. The residue was diluted in anhydrous THF (10 ml) and 1-ethylpiperazine (1 ml) was added to the previous solution. The reaction mixture was stirred at room temperature for 1 h, then the solvent was removed under vacuum and water poured into the residue. The resulting mixture was extracted with diethyl ether. The combined organic phases were thoroughly washed with water and an aqueous solution of $NaHCO_3$, dried over Na_2SO_4 and evaporated to give a residue, which was further purified by flash column chromatography, using as eluent a mixture of DCM:EtOAc, 2:1 to afford 218 mg of an oily product (yield 45%). ^{1}H-NMR (400MHz, $CDCl_3$) δ 0.97-1.01(t, 3H, A_3X_2, J_{AX}=7Hz, CH_3CH_2), 0.98-1.07(m, 2H, β-H), 1.48-1.55(m, 6H, 2, 8, 9-H), 1.70(br.s, 6H, 4, 6, 10-H), 1.87(br.s, 3H, 3, 5, 7 -H), 1.98-2.03(~t, 2H, J~8Hz, γ-H), 2.12-2.15(~t, 2H, J~7.8 Hz, α-H), 2.09-2.56(very br.s, 8H, 2, 3, 5, 6-Hp), 2.30-2.35(t, 2H, A_3X_2, J_{AX}=7 Hz, CH_3CH_2) 7.09-7.17(m, 6H, 2, 4, 6 -Har), 7.24-7.26(~d, 4H, J~7.5 Hz, 3, 5-Har); ^{13}C-NMR (100MHz, $CDCl_3$) δ 11.82(CH_3), 23.0(β-C), 29.4(3, 5, 7-C), 36.6(γ-C), 36.9(2, 8, 9-C), 38.9(4, 6, 10-C), 40.1(1-C), 52.5(3, 5-Cp), 52.6(CH_2CH_3), 55.0(2, 6-Cp) 58.2(δ-C), 59.3(α-C), 125.3(4-Car), 126.6(2, 6-Car), 131.2(3, 5-Car), 145.1(1-Car). Dihydrochloride: Mp 229-231 ^{o}C (EtOH-Et_2O); Anal. Calcd for $C_{32}H_{46}Cl_2N_2 \cdot H_2O$, C: 70.18; H: 8.84; N: 5.12. Found C: 70.14; H: 8.58; N: 5.43.

1-Benzyl-4-[4,4–diphenyl-4-(1-tricyclo[3.3.1.1.^{3,7}]decyl) butyl]piperazine (1c)

Piperazine **1c** was synthesized in a similar way to pirerazine **1b**, using butatol **7a** as starting material. Yield 75%

of an oily product. ^{1}H-NMR(400MHz, $CDCl_3$) δ 0.96-1.09(m, 2H, β-H), 1.45-1.57(m, 6H, 2, 8, 9-H), 1.69(br.s, 6H, 4, 6, 10-H), 1.86(br.s, 3H, 3, 5, 7-H), 1.99-2.02(~t, 2H, *J*~7.8Hz, γ-H), 2.10-2.14(~t, 2H, *J*~7.8Hz, α-H), 2.07-2.51(very br.s, 8H, 2, 3, 5, 6-Hp), 3.40(s, 2H, β-H), 7.08-7.15(m, 9H, 2, 4, 6, 2`, 4`, 6`-Har), 7.21-7.26(m, 6H, 3, 5, 3`, 5`-Har); $^{13}$C-NMR(100MHz, $CDCl_3$) $\delta$ 23.0($\beta$-C), 29.4(3, 5, 7-C), 33.6($\gamma$-C), 36.9(2, 8, 9 -C), 38.9(4, 6, 10-C), 53.0(3, 5-Cp), 53.2(2, 6-Cp) 57.6($\delta$-C), 59.4($\alpha$-C), 63.0($\beta$-C), 125.3(4-Car), 126.5(2, 6-Car), 126.9(4`-Car), 128.1(2`, 6`-Car), 129.2(3`, 5`-Car), 131.2(3, 5-Car), 138.1(1`-Car), 145.1(1-Car); Difumarate: Mp 227-229 ^{o}C (EtOH-Et_2O); Dipicrate: Mp 248 ^{o}C (acetone); Anal. Calcd for $C_{49}H_{52}N_8O_{14}$, C: 60.24; H: 5.37; Found C: 60.26; H: 5.46.

1-Cyclohexyl-4-[4,4–diphenyl-4-(1-tricyclo[3.3.1.1.^{3,7}] decyl)butyl]piperazine (1d)

Piperazine **1d** was synthesized in a similar way to pirerazine **1b** using butatol **7a** as starting material. Yield 66% of an oily product. ^{1}H-NMR(400MHz, $CDCl_3$) δ 1.05-1.25(complex m, 7H, β -H, 2, 3, 4, 5, 6-Hc,ax), 1.54-1.61(m, 6H, 2, 8, 9-H), 1.76(br.s, 6H, 4, 6, 10-H), 1.84-1.86(m, 5H, 2, 3, 4, 5, 6-Hc,eq), 1.93(br.s, 3H, 3, 5, 7-H), 2.05-2.09(~t, 2H, *J*~8Hz, γ-H), 2.18-2.20(m, 3H, α-H, 1-Hc,ax), 2.25-2.43(br.s, 4H, 3, 5-Hp), 2.45-2.62(br.s, 4H, 2, 6 -Hp), 7.15-7.22(m, 6H, 2, 4, 6-Har), 7.30-7.32(~d, 4H, *J*=7Hz, 3, 5 -Har); ^{13}C-NMR(100MHz, $CDCl_3$) δ (ppm): 23.0(β-C), 25.833, 5-Cc), 26.2(4-Cc), 28.9(2, 6-Cc), 29.4(3, 5, 7-C), 33.6(γ-C), 36.9(2, 8, 9-C), 38.8(4, 6, 10-C), 40.1(1-C), 48.8(2, 6-Cp), 53.6(3, 5-Cp) 58.2(δ-C), 59.5(α-C), 63.5(1-Cc), 125.2(4-Car), 126.5(2, 6-Car), 131.2(3, 5-Car), 145.1(1-Car); Dihydrochloride: Mp 260-262 ^{o}C (EtOH-Et_2O); Anal. Calcd for $C_{36}H_{52}Cl_2N_2{\cdot}H_2O$, C: 71.85; H: 9.05; N: 4.66. Found C: 71.50; H: 9.34; N:4.66.

1-[4,4–Diphenyl-4-(1-tricyclo[3.3.1.1.^{3,7}]decyl)butyl]piperazine (1e)

To a stirred suspension of *N*-benzyl derivative **1d** (1.06 g, 2 mmol) and Pd/C (10%, 950 mg) in methanol (20 ml) was added at once ammonium formate (621 mg, 10 mmol) under an argon atmosphere. The reaction mixture was heated at reflux for 3 h and then cooled to r.t. The catalyst was filtered off through Celite and the filtrate was evaporated *in vacuo* to give a residue, which was purified by flash column chromatography, using as eluent a mixture of $CHCl_3$:MeOH, 9:1 to afford 781 mg of crystalline product (Yield 89%). Mp 76-78 ^{o}C; ^{1}H-NMR(400MHz, $CDCl_3$) δ (ppm): 0.97-1.00(m, 2H, β-H), 1.46-1.56(m, 6H, 2, 8, 9 -H), 1.66(br.s, 6H, 4, 6, 10-H), 1.83(br.s, 3H, 3, 5, 7-H), 1.96- 2.00(~t, 2H, *J*~7.8Hz, γ-H), 2.07-2.11(t, 2H, *J*~7.5Hz, α-H), 2.22(br.s, 4H, 2, 6 -Hp), 2.79-2.81(t, 4H, *J*~4.8Hz, 3, 5 -Hp), 2.95-3.50(very br.s, 1H, NH), 7.06-7.16(m, 6H, 2, 4, 6-Har), 7.21-7.23(~d, 4H, *J*~7.5Hz, 3, 5-Har); ^{13}C-NMR(100MHz, $CDCl_3$) δ (ppm): 22.8(β -C), 29.4(3, 5, 7 -C), 33.5(γ -C), 40.0(2, 8, 9 -C), 38.9(4, 6, 10-C), 40.2(1-C), 45.2(3, 5-Cp), 53.1(2, 6 -Cp) 58.3(δ -C), 59.5(α-C), 125.3(4-Car), 126.6(2, 6-Car), 131.2(3, 5-Car), 145.1(1-Car); Difumarate: Mp 188-190 ^{o}C (EtOH-Et_2O); Dipicrate: Mp >250 ^{o}C (acetone); Anal. Calcd for $C_{42}H_{46}N_8O_{14}$, C: 56.88; H: 5.23; N: 12.63. Found C: 56.59; H: 5.19; N: 12.75.

4-[4,4–Bis-(4-methylphenyl-4-(1-tricyclo[3.3.1.1.^{3,7}]decyl) butyl]-1-methylpiperazine (1f)

Piperazine **1f** was synthesized in a similar way to pirerazine **1b** using butatol **7f** as starting material. Yield 34% of an oily product. ^{1}H-NMR(400MHz, $CDCl_3$) δ (ppm): 1.04-1.21(m, 2H, β -H), 1.55-1.62(m, 6H, 2, 8, 9-H), 1.76(br.s, 6H, 4, 6, 10-H), 1.93(br.s, 3H, 3, 5, 7-H), 2.02- 2.06(~t, 2H, *J*~4Hz, γ-H), 2.18-2.22(t, 2H, *J*~7.5Hz, α-H), 2.25(s, 3H, CH_3-N), 2.32(s, 6H, 4ar -CH_3), 2.23-2.60(very br.s, 8H, 2, 3, 5, 6-Hp), 7.01-7.03(d, 4H, AA`BB`, J_{AB}=$J_{A`B`}$=8Hz, $J_{AA`}$=$J_{BB`}$=0Hz, 2, 6-Har), 7.20-7.22(d, 4H, AA`BB`, J_{AB}=$J_{A`B`}$=8Hz, $J_{AA`}$=$J_{BB`}$=0Hz, 3, 5 -Har); ^{13}C-NMR(100MHz, $CDCl_3$) δ (ppm): 20.8(4ar -C), 23.0(β -C), 29.4(3, 5, 7 -C), 33.6(γ-C), 37.0(2, 8, 9-C), 38.8(4, 6, 10 -C), 40.1(1-C), 45.98(CH_3-N), 53.15(3, 5-Cp), 55.04(2, 6-Cp) 57.48(δ-C), 59.36(α-C), 127.2(3, 5-Car), 131.1(2, 6-Car), 134.5(4-Car), 142.0(1-Car); Dihydrochloride: Mp > 250 ^{o}C (EtOH-Et_2O); Anal. Calcd for $C_{33}H_{48}Cl_2N_2{\cdot}1/2H_2O$, C: 71.72; H: 8.93; N: 5.07. Found C: 71.59; H: 8.96; N: 5.12.

4-[4,4–Bis-(4-methoxyphenyl-4-(1-tricyclo[3.3.1.1.^{3,7}]decyl)butyl]-1-methylpiperazine (1g)

Piperazine **1g** was synthesized in a similar way to pirerazine **1a** using butatol **7g** as starting material. Purification by flash column chromatography, using as eluent a mixture of DCM:EtOAc, 2:1 gave compound **1g** as a solid. Yield 42%. Mp 30-32 ^{o}C; ^{1}H-NMR(400MHz, $CDCl_3$) δ (ppm): 0.96-1.04(m, 2H, β-H), 1.46-1.54(m, 6H, 2, 8, 9-H), 1.65(br.s, 6H, 4, 6, 10 -H), 1.85(br.s, 3H, 3, 5, 7-H), 1.92-1.96(t, 2H, *J*~7.5- 8Hz, γ-H), 2.10-2.14(t, 2H, J~7.6Hz, α-H), 2.17(s, 3H, CH_3-*N*), 2.12-2.51(very br.s, 8H, 2, 3, 5, 6-Hp), 3.72(s, 6H, OCH_3), 6.67-6.69(d, 4H, AA`BB`, J_{AB}=$J_{A`B`}$=9 Hz, $J_{AA`}$=$J_{BB`}$=0 Hz, 3, 5-Har), 7.14-7.17(d, 4H, AA`BB`, J_{AB}=$J_{A`B`}$=9 Hz, $J_{AA`}$=$J_{BB`}$=0 Hz, 2, 6 -Har); ^{13}C-NMR(100MHz, $CDCl_3$) δ (ppm): 23.0(β,-C), 29.4(3, 5, 7-C), 33.7(γ-C), 37.0(2, 8, 9-C), 38.8(4, 6, 10-C), 40.3(1-C), 46.0(CH_3-*N*), 53.2(3, 5 -Cp), 55.1(2, 6-Cp, OCH_3), 56.9(δ-C), 59.4(α-C), 111.8(3, 5-Car), 132.1(2, 6-Car), 137.2(1-Car), 156.9(4-Car); Dihydrochloride: Mp 222-225 ^{o}C(EtOH-Et_2O); Anal. Calcd for $C_{33}H_{48}Cl_2N_2O_2{\cdot}H_2O$, C: 66.76; H: 8.49; N: 4.72. Found C: 66.90; H: 8.63; N: 4.80.

4-[4,4–Bis-(4-fluorophenyl)-4-(1-tricyclo[3.3.1.1.^{3,7}]decyl) butyl]-1-methylpiperazine (1h)

Piperazine **1h** was synthesized in a similar way to pirerazine **1b** using butatol **7h** as starting material. Yield 55% of an oily product. ^{1}H-NMR(400MHz, $CDCl_3$) δ (ppm): 0.94-1.01(m, 2H, β-H), 1.47-1.56(m, 6H, 2, 8, 9-H), 1.65(br.s, 6H, 4, 6, 10-H), 1.87(br.s, 3H, 3, 5, 7-H), 1.95-1.99(~t, 2H, *J*~6.5= 8 Hz, γ-H), 2.11-2.15(~t, 2H, *J*~7.5Hz, α-H), 2.08-2.52(very br.s, 8H, 2, 3, 5, 6 -Hp), 2.19(s, 3H, CH_3), 6.82-6.87(~t, 4H, $J_{2ar,3ar}$ ~ $J_{3ar,F}$= 8.6 Hz, $J_{3ar,5ar}$=0 Hz, 3, 5-Har), 7.17-7.20(~q, 4H, $J_{2ar,3ar}$=8.6 Hz, $J_{2ar,F}$=3.5 Hz, $J_{2ar,6ar}$=0 Hz, 2, 6-Har); ^{13}C-NMR(100MHz, $CDCl_3$) δ (ppm): 23.1(β -C), 29.3(3, 5, 7-C), 33.9(γ-C), 36.9(2, 8, 9-C), 38.8(4, 6, 10-C), 40.2(1-C), 46.0(CH_3), 53.2(3, 5-Cp), 55.1(2, 6 -Cp), 57.4(δ -C), 59.2(α-C), 113.3, 113.5(3, 5-Car), 132.4, 132.5(2-Car), 140.6(1-Car), 159.4, 161.9(4-Car); Difumarate: Mp 219-220 ^{o}C (EtOH-Et_2O); Anal. Calcd for

$C_{39}H_{48}F_2N_2O_8$, C: 65.90; H: 6.81; N: 3.94. Found C: 65.73; H: 6.88; N: 4.01.

1-Methyl-4-[4–(methylphenyl)-4-phenyl-4-(1-tricyclo[3.3.1.1.^{3,7}]decyl)butyl]piperazine (1i)

Piperazine **1i** was synthesized in a similar way to pirerazine **1b** using butatol **7i** as starting material. Yield 51% of an oily product. ^{1}H-NMR(400MHz, $CDCl_3$) δ (ppm): 0.95-1.03(m, 2H, *β* -H), 1.45-1.53(m, 6H, 2, 8, 9-H), 1.67(br.s, 6H, 4, 6, 10 -H), 1.83(br.s, 3H, 3, 5, 7 -H), 1.95- 1.98(m, 2H, *γ*-H), 2.08-2.12(~t, 2H, *J*~8Hz, *α*-H), 2.04-2.52(very br.s, 8H, 2, 3, 5, 6 -Hp), 2.15(s, 3H, CH_3-*N*), 6.92-6.94(~d, 2H, *J*=8.5Hz, 3, 5 -Har), 7.04-7.13(m, 5H, 2, 6-Har, 3`, 4`, 5`-Har), 7.22-7.24(~d, 2H, *J*=7.5Hz, 2`, 6`-Har); $^{13}$C-NMR(100MHz, $CDCl_3$) δ (ppm): 20.8($CH_3$), 23.0(*β*-C), 29.4(3, 5, 7 -C), 33.6(*γ*-C), 37.0(2, 8, 9-C), 38.9(4, 6, 10-C), 40.2(1-C), 45.9($CH_3$-*N*), 53.1(3, 5 -Cp), 55.0(2, 6-Cp) 57.9(*δ*-C), 59.3(*α* -C), 125.2(4`-Car), 126.5(3`, 5`-Car), 127.3(3, 5-Car), 131.1(2, 6-Car), 134.6(4-Car), 141.9(1`-Car), 145.2(1-Car); Dihydrochloride: Mp 247-248 ^{o}C (EtOH-Et_2O); Anal. Calcd for $C_{32}H_{46}Cl_2N_2 \cdot H_2O$, C: 70.18; H: 8.83; N: 5.12. Found C: 70.54; H: 8.89; N: 5.20.

1-[4,4–Diphenyl-4-(1-tricyclo[3.3.1.1.^{3,7}]decyl)butyl]piperidine (1j)

Piperidine **1j** was synthesized in a similar way to pirerazine **1b** using butatol **7a** as starting material. Purification by flash column chromatography, using as eluent a mixture of DCM:EtOAc, 2:1 gave an oily product. Yield 40%. ^{1}H-NMR(400MHz, $CDCl_3$) δ (ppm): 1.13-1.21(m, 2H, *β*-H), 1.37(br.s, 2H, 4-Hp), 1.51-1.54(m, 4H, 3, 5-Hp), 1.59(m, 6H, 2, 8, 9-H), 1.77(br.s, 6H, 4, 6, 10-H), 1.93(br.s, 3H, 3, 5, 7-H), 2.06- 2.10(~t, 2H, *J*~8Hz, *γ*-H), 2.15-2.19(~t, 2H, *J*~7.8Hz, *α*-H), 2.24(br.s, 4H, 2, 6-Hp), 7.15-7.23(m, 6H, 2, 4, 6 -Har), 7.32-7.34(d, 4H, *J*=7.6Hz, 3, 5 -Har); ^{13}C-NMR(100MHz, $CDCl_3$) δ (ppm): 22.8(*β* -C), 24.2(4-C), 25.6(3, 5-Cp), 29.4(3, 5-C), 33.7(*γ* -C), 36.9(2, 8, 9-C), 38.8(4, 6, 10-C), 40.1(1-C), 54.4(2, 6 -Cp), 58.2(*δ*-C), 60.0(*α*-C), 125.2(4-Car), 126.5(2, 6-Car), 131.2(3, 5-Car), 145.1(1-Car); Hydrochloride: Mp >250 ^{o}C (EtOH-Et_2O); Anal. Calcd for $C_{31}H_{42}ClN$, C: 80.22; H: 9.12; N: 3.02. Found C: 79.95; H: 9.22; N: 3.14.

N,N-Dimethyl-4,4–diphenyl-4-(1-tricyclo[3.3.1.1.^{3,7}]decyl) butylamine (1k)

A solution of the tosylate of butanol **7a** (580 mg, 11.3 mmol) and a solution of dimethylamine in ethanol (5.6 ml, 2 M, 11.3 mmol) was heated to reflux for 3 h. The reaction mixture was worked up as reported for amine **1a** (tosylate method). Purification by flash column chromatography, using as eluent $CHCl_3$: MeOH, 9 :1, afforded 372 mg of **1k** (Yield 85%).^{1}H-NMR (400MHz, $CDCl_3$) δ (ppm): 1.10(br.s, 2H, *β*-H), 1.53-1.62(br.m, 6H, 2, 8, 9-H), 1.62(br.s, 6H, 4, 6, 10-H), 1.93-1.97(m, 5H, 3, 5, 7, *γ*-H), 2.68(s, 6H, $(CH_3)_2$N), 2.68-2.73(m, 2H, *α*-H), 7.16-7.28(m, 10H, 2xC_6H_5). ^{13}C-NMR(100MHz, $CDCl_3$) δ (ppm): 18.2(*β*-C), 28.4(3, 5, 7-C), 31.1(*γ*-C), 35.9(2, 8, 9 -C), 38.0(4, 6, 10-C), 39.5(1 -C), 49.4(CH_3-N), 57.6(*δ*-C), 63.2(*α*-C), 125.0(4-Car), 126.2(2, 6 -Car), 130.0(3, 5-Car), 143.2(4-Car); Hydrochloride: Mp 261-263^{o}C(EtOH); Anal. Calcd for $C_{28}H_{38}ClN$, C: 79.30; H: 9.05; N: 3.30. Found C: 78.98; H: 9.26; N: 3.29.

δ,δ-Diphenyl-*δ*-(1-tricyclo[3.3.1.1.^{3,7}]decane)butanol methanesulfonate (10)

To a stirred solution of butanol **7a** (1.0 g, 2.77 mmol) in a mixture of pyridine (1.5 ml) and anhydrous DCM (1.5 ml) was added dropwise a solution of mesylchloride (1.35 g, 12 mmol) in anhydrous DCM (1.5 ml) at 0 ^{o}C. The reaction mixture was stirred for 12h at rt, then treated with chilled water for 30 min. The mixture was extracted with DCM. The combined organic phases were washed with 2N HCl, 5% $NaHCO_3$ and water, dried over Na_2SO_4 and the solvent evaporated in vacuo. The residue was further purified by flash column chromatography, using DCM as eluent to give 1.2 g (yield almost quantitative) of a white solid. Mp 136-138 ^{o}C; ^{1}H-NMR (400MHz, $CDCl_3$) *δ* (ppm): 1.30-1.34(m, 2H, *β*-H), 1.52-1.54(m, 6H, 2, 8, 9-H), 1.70(br.s, 6H, 4, 6, 10 -H), 1.88(br.s, 3H, 3, 5, 7-H), 2.12-2.16(m, 2H, *γ*-H), 2.86(s, 3H, CH_3), 3.94-3.97(t, 2H, J=6,4Hz, *α*-H), 7.13-7.20(m, 6H, 2, 4, 6-Har), 7.25-7.27(m, 4H, 3, 5-Har).

δ,δ-Diphenyl-1-tricyclo[3.3.1.1.^{3,7}]decanepentanonitrile (11)

Sodium cyanide (750 mg, 15 mmol) was added to a solution of mesylate **10** (2.1 g, 4.8 mmol) in DMSO (10 ml) and the mixture was stirred under an argon atmosphere at 60 ^{o}C for 12h. After cooling the reaction mixture was poured into chilled water and extracted with ethyl acetate. The combined organic phases were washed with water, dried over Na_2SO_4 and the solvent evaporated *in vacuo*. The residue was further purified by flash column chromatography using as eluent a mixture of *n*-hexane : ether, 4:1, to give 1.6 g (yield 40%) of a solid product. Mp 139-141 ^{o}C. IR (Nujol) v (CN) 2244 cm^{-1}; ^{1}H-NMR(400MHz, $CDCl_3$) δ(ppm): 1.14-1.18(m, 2H, *β*-H), 1.45-1.57(m, 6H, 2, 8, 9-H), 1.65(br.s, 6H, 4, 6, 10-H), 1.83(br.s, 3H, 3, 5, 7-H), 1.99-2.03(t, 2H, *J*=7Hz, *α*-H), 2.10-2.14(m, 2H, *γ*-H), 7.05-7.14(m, 6H, 2,4,6-Har), 7.18-7.21(m, 4H, 3,5-Har). ^{13}C-NMR(100MHz, $CDCl_3$) δ (ppm): 17.6(*α*–C), 22.0(*β*-C), 29.3(3, 5, 7-C), 35.1(*γ*-H), 36.8(2, 8, 9-C), 38.8(4, 6, 10-C), 40.2(1-C), 58.0(*δ*-C), 119.8(CN), 125.6(4-Car), 126.8(2, 6-Car), 131.0(3, 5-Car), 144.3(1-Car). Anal. Calcd for $C_{27}H_{31}N$, C: 87.75; H: 8.46; Found C: 87.90; H: 8.26;

Ethyl *δ,δ*-diphenyl-1-tricyclo[3.3.1.1.^{3,7}]decanepentanoate (12)

Carbonitrile **11** (2.0 g, 6.4 mmol) was added to a mixture of saturated ethanolic hydrogen chloride (15 ml) and absolute ethanol (10 ml). The reaction mixture was heated to reflux for 2 h, water (9 drops) was then added and heating was continued for 1 h. Ethanol was removed *in vacuo*, water was added to the residue and the mixture was extracted with ether. The organic phase was washed with water, saturated solution of Na_2CO_3 (10%), dried over Na_2SO_4 and the solvent evaporated under vacuum. The residue was further purified by flash column chromatography, using as eluent a mixture of *n*-hexane : ether, 2:1, to give 1.5 g (yield 67%) of a solid product. Mp 61-63 ^{o}C. IR (Nujol) v (C=O) 1731cm^{-1}; ^{1}H-NMR(400MHz, $CDCl_3$) δ(ppm): 1.13-1.21(m, 2H, *β*-H),

1.14-1.71(t, 3H, A_3X_2, J_{AX}=7Hz,CH_3CH$_2$), 1.48-1.55(m, 6H, 2, 8, 9-H), 1.70(br.s, 6H, 4, 6, 10-H), 1.86(br.s, 3H, 3, 5, 7-H), 2.02-2.07(m, 2H, γ-H), 2.09-2.10(~t, 2H, J=4Hz, α-H), 3.99-4.04(q, 2H, A_3X_2, J_{AX}=7Hz, CH$_3$CH_2), 7.10-7.18(m, 6H, 2,4,6-Har), 7.26-7.28(m, 4H, 3,5-Har). ^{13}C-NMR(100MHz, $CDCl_3$) δ (ppm): 14.24(CH_3), 21.3(β-C), 29.4(3, 5, 7-C), 34.9(α-H), 35.4(γ-C), 36.9(2, 8, 9-C), 38.8(4, 6, 10-C), 40.2(1-C), 58.2(δ-C), 60.1(CH$_3$CH_2), 125.3(4-Car), 126.6(2, 6-Car), 131.3(3, 5-Car), 144.9(1-Car), 173.6(C=O). Anal. Calcd for $C_{29}H_{36}O_2$, C: 83.61; H: 8.71. Found C: 84.00; H: 8.81.

1-Methyl-4-(δ,δ-diphenyl-1-tricyclo[3.3.1.1.^{3,7}]decyl-pentanoyl)piperazine (13a)

To a stirred solution of ethyl ester **12** (680 mg, 1.6 mmol) in ethanol (10 ml) was added a solution of NaOH (2.0 g, 50 mmol) in a minimum amount of water and the mixture was refluxed for 2 h. Ethanol was then evaporated, water was added to the residue and the resulting mixture was acidified with HCl 10% under cooling. The mixture was extracted with ether and the organic phase was washed with water, dried over Na_2SO_4 and concentrated in vacuo. Thionyl chloride (3 ml) was then added to the residue and the resulting mixture was refluxed gently for 1 h. The excess of thionyl chloride was removed *in vacuo* and the last traces with the aid of anhydrous benzene. The residue was dissolved in THF (10 ml) and the resulting solution was added dropwise to a stirred solution of 1-methylpiperazine (3 ml) in THF (10 ml) under cooling. The reaction mixture was refluxed for 3 h and the solvent was removed under vacuum. Water was added to the residue and the mixture was extracted with DCM. The combined organic phases were washed with water, dried over Na_2SO_4 and evaporated in vacuo to give a residue, which was purified by flash column chromatography, using as eluent a mixture of chloroform : methanol, 9:1, to give 620 mg (yield 90%) of a semisolid product. IR (Nujol) v (C=O) 1652 cm^{-1}; ^{1}H-NMR(400MHz, $CDCl_3$) δ(ppm): 1.15-1.22(m, 2H, β-H), 1.46-1.58(m, 6H, 2, 8, 9-H), 1.70(br.s, 6H, 4, 6, 10-H), 1.82(br.s, 3H, 3, 5, 7-H), 2.06-2.10(m, 4H, α, γ-H), 2.14-2.16(t, 2H, 2-Hp), 2.23-2.25(t, 2H, 6-Hp), 3.14-3.17(t, 2H, J=5Hz, 3-Hp), 3.48-3.51(~t, 2H, 5-Hp), 7.07-7.19(m, 6H, 2,4,6-Har), 7.27-7.29(m, 4H, 3,5-Har). ^{13}C-NMR(100MHz, $CDCl_3$) δ (ppm): 21.8(β-C), 29.4(3, 5, 7-C), 34.3(α-C), 35.8(γ-C), 36.9(2, 8, 9-C), 38.9(4, 6, 10-C), 40.2(1-C), 41.2(5-Cp), 45.3(3-Cp), 45.9(CH_3), 54.6(2-Cp), 55.0(6-Cp), 58.4(δ-C), 125.3(4-Car), 126.6(2, 6-Car), 131.3(3, 5-Car), 154.0(1-Car), 171.3(C=O). Anal. Calcd for $C_{32}H_{42}N_2O$, C: 81.66; H: 8.99; N: 5.95. Found C: 81.60; H: 9.00; N: 5.99.

1-(δ,δ-Diphenyl-1-tricyclo[3.3.1.1.^{3,7}]decanepentanoyl) piperidine (13b)

Amide **13b** was prepared from the ester **12** in a similar way to amide **13a** and was purified by flash column chromatography, using as eluent a mixture of chloroform : methanol, 9:1. Yield 90% of solid product. Mp 130-132 ^{o}C; IR (Nujol) v (C=O) 1638 cm^{-1}; ^{1}H-NMR(400MHz, $CDCl_3$) δ(ppm): 1.16-1.21(m, 2H, β-H), 1.30(br.s, 2H, 4-Hp), 1.36(br.s 2H, 5-Hp),1.49-1.54(m, 8H, 2, 8, 9-H, 3-Hp), 1.70(br.s, 6H, 4, 6, 10-H), 1.86(br.s, 3H, 3, 5, 7-H), 2.07-2.10(m, 4H, α, γ-H), 3.09(br.s, 2H, 6-Hp), 3.40(br.s, 2H, 2-Hp), 7.07-7.20(m, 6H, 2,4,6-Har), 7.27-7.29(m, 4H, 3,5-Har). ^{13}C-NMR(100MHz, $CDCl_3$) δ (ppm): 21.9(β-C), 24.5(3-Cp), 25.5(5-Cp), 26.4(4-Cp), 26.4(3, 5, 7-C), 34.5(α-C), 35.8(γ-C), 36.5(2, 8, 9-C), 38.8(4, 6, 10-C), 40.1(1-C), 42.4(2-Cp), 46.6(6-Cp), 54.6(2-Cp), 58.4(δ-C), 125.3(4-Car), 126.6(2, 6-Car), 131.3(3, 5-Car), 145.0(1-Car), 171.2(C=O). Anal. Calcd for $C_{32}H_{41}NO$ C: 84.35; H: 9.07; N: 3.07. Found C: 84.65; H: 9.05; N: 3.00.

1-Methyl-4-[5,5-diphenyl-(1-tricyclo[3.3.1.1.^{3,7}]decyl) pentyl]piperazine (2a)

To a stirred suspension of $LiAlH_4$ (500 mg) in anhydrous THF (20 ml) was added dropwise a solution of amide **13a** (500 ml, 1.06 mmol) in anhydrous THF (10 ml). The reaction mixture was refluxed for 3 h, then hydrolysed by adding ethanol, water and a solution of NaOH 10% at 0 ^{o}C. The inorganic material was filtered and the filtrate was evaporated. Water was added to the residue and the resulting mixture was extracted with DCM. The combined organic phases were washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to give 400 mg (yield 83%)of a low mp solid. ^{1}H-NMR(400MHz, $CDCl_3$) δ(ppm): 0.80-0.86(m, 2H, γ-H), 1.31-1.35(m, 2H, β-Hp), 1.48-1.55(m, 6H, 2, 8, 9-H), 1.69(br.s, 6H, 4, 6, 10-H), 1.87(br.s, 3H, 3, 5, 7-H), 2.01-2.05(t, 2H, J=7.5Hz, δ-H), 2.11-2.15(t, 2H, J=7.5Hz, α-H), 2.21(s, 3H, CH_3), 2.05-2.60(very br.s, 8H, 2, 3, 5, 6-Hp), 7.08-7.17(m, 6H, 2,4,6-Har), 7.23-7.25(m, 4H, 3,5-Har). ^{13}C-NMR(100MHz, $CDCl_3$) δ (ppm): 23.7(γ-C), 27.7(β-C), 29.4(3, 5, 7-C), 35.8(δ-C), 36.9(2, 8, 9-C), 38.8(4, 6, 10-C), 40.1(1-C), 45.9(CH_3), 52.9(3,5-Cp), 54.9(2, 6-Cp), 58.3(ε-C), 58.3(α-C), 125.2(4-Car), 126.5(2, 6-Car), 131.3(3, 5-Car), 145.2(1-Car). Dihydrochloride Mp>250 ^{o}C (EtOH-Et_2O), Anal. Calcd for $C_{32}H_{46}Cl_2N_2.H_2O$, C: 70.05; H: 9.00; N: 5.11. Found C: 69.74; H: 8.90; N: 5.01.

1-[5,5-diphenyl-(1-tricyclo[3.3.1.1.^{3,7}]decyl)pentyl]piperidine (2b)

Pentylamine **2b** was prepared by reduction of amide **13b** with $LiAlH_4$ in a similar way to pentylamine **2a**. Yield almost quantitative of a viscous oil. ^{1}H-NMR(400MHz, $CDCl_3$) δ(ppm): 0.75-0.86(m, 2H, γ-H), 1.30-1.36(m, 4H, β-Hp, 4-Hp), 1.48-1.58(m, 10H, 2, 8, 9-H, 3, 5-Hp), 1.69(br.s, 6H, 4, 6, 10-H), 1.86(br.s, 3H, 3, 5, 7-H), 2.01-2.09(m, 4H, α, δ-H), 2.20-2.32(m, 4H, 2, 6-Hp), 7.10-7.19(m, 6H, 2,4,6-Har), 7.24-7.26(m, 4H, 3,5-Har). ^{13}C-NMR(100MHz, $CDCl_3$) δ (ppm): 23.0(γ-C), 23.5(4-Cp), 24.9(3,5-Cp), 28.5(3, 5, 7-C), 29.4(β-C), 35.0(δ-C), 36.0(2, 8, 9-C), 37.9(4, 6, 10-C), 39.2(1-C), 53.6(2,6-Cp), 57.4(ε-C), 58.3(α-C), 124.3(4-Car), 125.6(2, 6-Car), 130.4(3, 5-Car), 144.3(1-Car). Hydrochloride Mp>250 ^{o}C (EtOH-Et_2O), Anal. Calcd for $C_{32}H_{44}Cl_2N.1/2H_2O$, C: 78.89; H: 9.31; N: 2.88. Found C: 79.20; H: 9.14; N: 2.92.

γ,γ-Diphenyl-1-tricyclo[3.3.1.1.^{3,7}]decanebutanal (14)

To a solution of alcohol **7a** (925 mg, 2.65 mmol) in DCM (5.3 ml) PCC (858 mg, 3.98 mmol) was added. The reaction mixture was stirred at r.t. for 2h, then ether was added, the mixture was filtered through a short pad of florisil and washed with ether. The filtrate was evaporated to afford 800 mg (yield 87%) of a white amorphous solid, which was used

to the next step without further purification. Mp 156-158 °C. IR (KBr) v (C=O) 1717 cm^{-1}; ^{1}H-NMR(400MHz, $CDCl_3$) δ(ppm): 1.49-1.56(m, 6H, 2, 8, 9-H), 1.71-1.72(m, 6H, 4, 6, 10-H), 1.89(br.s, 3H, 3, 5, 7-H), 2.06-2.10(t, 2H, A_2X_2, *J*=7.5Hz, *β*-H), 2.39-2.43(t, 2H, A_2X_2, *J*=7.5Hz, *α*-H), 7.10-7.19(m, 6H, 2,4,6-Har), 7.24-7.26(m, 4H, 3,5-Har), 9.42(s, 1H,CH=O). ^{13}C-NMR(100MHz, $CDCl_3$) δ (ppm): 27.8(*α*-C), 29.3(3, 5, 7-C), 36.9(2, 8, 9-C), 38.9(4, 6, 10-C), 40.7(1-C), 41.6(*β*-C), 57.6(*γ*-C), 125.7(4-Car), 126.9(2, 6-Car), 131.0(3, 5-Car), 144.3(1-Car), 202.4(C=O).

Ethyl (*E*)-*ε,ε*-diphenyl-1-tricyclo[3.3.1.1.^{3,7}]decanehex-*α*-enoate (15)

To a stirred suspension of sodium hydride (136 mg, 60% disp, 3.4 mmol) in dry THF (6 ml) was added triethyl phosphonoacetate (695 mg, 0.62 ml, 3.1 mmol) under an argon atmosphere at 0 ^{0}C. After 30 min a solution of the aldehyde **14** (1.07 g, 3.1 mmol) in dry THF (6 ml) was added into the reaction mixture, which was then stirred for 30 more minutes. The reaction was quenched by adding a saturated solution of NH_4Cl at 0 °C. The mixture was extracted with ether and the combined organic phases were washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was further purified by flash column chromatography, using as eluent a mixture of cyclohexane : ethyl acetate, 95:5, to give 1.15 g (yield 87%) of a white amorphus solid unsaturated ester. ^{1}H-NMR(400MHz, $CDCl_3$) δ(ppm):1.26-1.29(t, 3H, A_3X_2, *J*=6Hz, CH_3), 1.57-1.63(m, 6H, 2, 8, 9-H), 1.75-1.82(m, 8H, 4, 6, 10, *δ*-H), 1.95(br.s, 3H, 3, 5, 7-H), 2.23-2.26(~t, 2H, *γ*-H), 4.14-4.18(q, 2H, A_3X_2, *J*=6Hz, CH_2O), 5.69-5.73(d, 1H, *J*=13Hz, *α*-H), 6.84-6.90(quin, 1H, *β*-H), 7.19-7.26(m, 6H, 2,4,6-Har), 7.31-7.33(m, 4H, 3,5-Har).

Ethyl *ε,ε*-diphenyl-1-tricyclo[3.3.1.1.^{3,7}]decanehexanoate (16)

To a solution of the olefinic ester **15** (540 mg, 1.26 mmol) in abs EtOH (40 ml) was added 10% Pd/C (60 mg) and the suspension stirred vigorously under hydrogen atmosphere, for 16h at rt. The catalyst was removed by filtration through celite, and the filtrate was evaporated under reduced pressure to give 542 mg of saturated ester **16**, as a white amorphous solid, which was used in the next step without further purification (Yield almost quantitative). Mp 75-77 °C. IR (KBr) v (C=O) 1716 cm^{-1}; ^{1}H-NMR(400MHz, $CDCl_3$) δ(ppm):0.82-0.91(m, 2H, *γ*-H), 1.10-1.13(t, 3H, A_3X_2, *J*=7Hz, CH_3), 1.42-1.55(complex m, 8H, 2, 8, 9, *β*-H), 1.69(br.s, 6H, 4, 6, 10-H), 1.87(br.s, 3H, 3, 5, 7-H), 2.01-2.05(m, 2H, *δ*-H), 2.06-2.10(t, 2H, A_2X_2, *J*=7.6Hz, *α*-H), 3.96-4.01(q, 2H, A_3X_2, *J*=7Hz, CH_2O), 7.07-7.18(m, 6H, 2,4,6-Har), 7.23-7.25(m, 4H, 3, 5-Har). ^{13}C-NMR(100MHz, $CDCl_3$) δ (ppm): 14.2(CH_3), 25.4(*γ*-C), 25.9(*β*-C), 29.4(3, 5, 7-C), 34.3(*a*-C), 35.7(*δ*-C), 36.9(2, 8, 9-C), 38.8(4, 6, 10-C), 40.1(1-C), 41.6(β-C), 58.2(*ζ*-C), 60.1(CH_2O), 125.3(4-Car), 126.9(2, 6-Car), 131.2(3, 5-Car), 145.1(1-Car), 173.7(C=O). Anal. Calcd for $C_{30}H_{38}O_2$, C: 83.67; H:8.89. Found C: 83.7; H:8.90.

ζ,ζ-Diphenyl-1-tricyclo[3.3.1.1.^{3,7}]decanehexanol (17)

To a stirred suspension of $LiAlH_4$ (185 mg, 4.26 mmol) in anhydrous THF (20 ml) was added dropwise a solution of ester **16** (493mg, 1.14 mmol) in anhydrous THF (10 ml). The reaction mixture stirred for 1 h at rt, then hydrolysed by adding ethanol, water and a solution of NaOH 10% at 0 °C. The inorganic material was filtered and the filtrate was evaporated. Water was added to the residue and the resulting mixture was extracted with ether. The combined organic phases were washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was further purified by flash column chromatography, using as eluent a mixture of cyclohexane : ethyl acetate, 80:20, to give 430 mg (yield 97%) of a white foam. Mp: 99-101 °C. IR (KBr) v (C=O) 3320 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$) δ(ppm): 0.81-0.89 (m, 2H, *δ*-H), 1.13-1.20(m, 2H, *γ*-H), 1.32(br.s, 1H, OH), 1.33-1.39(m, 2H, *β*-H), 1.49-1.58(m, 6H, 2, 8, 9- H), 1.70(br.s, 6H, 4, 6, 10-H), 1.86(br.s, 3H, 3, 5, 7-H), 2.00-2.04(m, 2H, *ε*-H), 3.42-3.45(t, 2H, *J*=6.5Hz, *α*-H), 7.10-7.17(m, 6H, 2, 4, 6 -Har), 7.24- 7.26(m, 4H, 3, 5-Har). ^{13}C-NMR (100MHz, $CDCl_3$) δ (ppm): 25.5(*δ*-C), 26.6(*γ*-C), 29.4(3, 5, 7-C), 32.6(*β*-C), 35.9(*ε*-C), 36.9(2, 8, 9-C), 38.9(4, 6, 10-C), 40.1(1-C), 58.3(*ζ*-C), 62.9(*α*-C), 125.2(4-Car), 126.5(2, 6- Car), 131.3(3,5-Car), 145.2(1-Car). Anal. Calcd for $C_{28}H_{36}O$, C: 86.54; H: 9.34. Found C: 86.68; H: 9.24.

4-[6,6-Diphenyl-6-(1-tricyclo[3.3.1.1.^{3,7}]decyl)hexyl]-1-methylpiperazine (3a)

To a stirred solution of hexanol **17** (384 mg, 0.99 mmol) in a mixture of pyridine (1.5 ml) and anhydrous DCM (1.5 ml) was added dropwise a solution of *p*-tosylchloride (226 mg, 1.19 mmol) in anhydrous DCM (1.5 ml) at 0 °C. The reaction mixture was stirred for 2 h at rt, then poured into chilled water and treated for 30 min. The mixture was extracted with DCM. The combined organic phases were washed with 2N HCl, 5% $NaHCO_3$ and water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography, using DCM as eluent to give 471 mg (yield 88%) of tosylate, as a white foam. The tosylate was dissolved in ethanol (10 ml) and the resulting solution was added dropwise to a stirred solution of 1-methylpiperazine (3 ml) in ethanol (10 ml) under cooling. The reaction mixture was refluxed for 5 h and the solvent was removed in vacuo. Water was added to the residue and the mixture was extracted with DCM. The combined organic phases were washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was further purified by flash column chromatography, using as eluent a mixture of dichloromethane : methanol, 95:5, to give 415 mg(yield 95%) of a viscous product. ^{1}H-NMR (400MHz, $CDCl_3$) δ(ppm): 0.38-0.90 (m, 2H, *δ*-H), 1.15-1.19(m,2H, *γ*-H), 1.32-1.38(m,2H, *β*-H), 1.55-1.63(m, 6H, 2, 8, 9- H), 1.76(br.s, 6H, 4, 6, 10-H), 1.93(br.s, 3H, 3, 5, 7-H), 2.05-2.10(m, 2H, *ε*-H), 2.19-2.22(~t, 2H, *α*-H), 2.27(t, 3H, CH_3), 2.01-2.65(very br.s, 8H, 2, 3, 5, 6-Hp), 7.14-7.23(m, 6H, 2, 4, 6-Har), 7.30- 7.32(m, 4H, 3, 5-Har). ^{13}C-NMR (100MHz, $CDCl_3$) δ (ppm): 25.6(*δ*-C), 26.7(*β*-C), 28.5(*γ*-C), 29.4(3,5,7-C), 35.9(*ε*-C), 37.0(2, 8, 9-C), 38.8(4, 6, 10-C), 40.1(1-C), 46.0(CH_3), 53.1(3, 5-Cp), 55.0(2, 6-Cp), 58.3(*ζ*-C), 58.7(*α*-C), 125.2(4-Car), 126.4(2, 6- Car), 131.3(3,5-Car), 145.2(1-Car). Dihydrochloride: Mp 245-247 °C (EtOH-Et_2O); Anal. Calcd for $C_{32}H_{46}Cl_2N_2.H_2O$, C: 70.18; H: 8.83; N: 5.12. Found C: 70.30; H: 8.63; N: 5.22.

1-[6,6-Diphenyl-6-(1-tricyclo[3.3.1.1.^{3,7}]decyl)hexyl]piperidine (3b)

A solution of tosylate (500 mg, 0.9 mmol) in ethanol (3 ml) and piperidine (3 ml) was refluxed for 5 h. The solvent was then removed in vacuo, water was added to the residue obtained and the mixture was extracted with DCM. The combined organic phases were washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was further purified by flash column chromatography, using as eluent a mixture of dichloromethane : methanol, 95:5, to give 415 mg (yield 99%) of a viscous product. ^{1}H-NMR (400MHz, $CDCl_3$) δ(ppm): 0.86-0.94(m, 2H, *δ*-H), 1.14-1.21(m, 2H, *γ*-H), 1.33-1.43(complex m, 4H, *β*-H, 4-Hp), 1.52-1.63(complex m, 10H, 2, 8, 9-H, 3, 5-Hp), 1.77(br.s, 6H, 4, 6, 10-H), 1.93(br.s, 3H, 3, 5, 7-H), 2.06-2.10(m, 2H, *ε*-H), 2.14-2.16(~t, 2H, *α*-H), 2.30(br.s, 4H, 3, 5-Hp), 7.14-7.23(m, 6H, 2, 4, 6-Har), 7.30- 7.32(m, 4H, 3, 5-Har). ^{13}C-NMR (100MHz, $CDCl_3$) δ (ppm): 24.4(4-Cp), 25.6(*δ*-C), 25.9(3, 5-Cp), 26.7(*β*-C), 28.6(*γ*-C), 29.4(3,5,7-C), 35.9(*ε*-C), 37.0(2, 8, 9-C), 38.8(4, 6, 10-C), 40.1(1-C), 54.5(2, 6-Cp), 58.3(ζ-C), 59.6(*α*-C), 125.2(4-Car), 126.4(2, 6- Car), 131.3(3,5-Car), 145.2(1-Car). Hydrochloride: Mp 241-242 ^{o}C (EtOH-Et_2O); Anal. Calcd for $C_{32}H_{44}ClN$, C: 80.38; H: 9.28; N: 2.93. Found C: 80.35; H: 9.48; N: 2.90.

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