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Design and synthesis of 3-phenyltetrahydronaphthalenic derivatives as new selective MT_2 melatoninergic ligands. Part II

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ABSTRACT

Following our studies of the melatoninergic receptors, we have developed new tetrahydronaphthalenic derivatives of melatonin that have been tested as selective melatonin receptors ligands. Regarding the role of the phenyl substituent to obtain selective ligands, modulation of selectivity and activity have been achieved by modifications of the acyl group and substitutions on the phenyl ring. Ten of the seventeen evaluated derivatives have MT_2 receptor affinity similar to that of melatonin. Moreover, we have achieved remarkable MT_2 selectivity over MT_1 (selectivity >100) and have been able to further extend the RSA of the tetrahydrophthalenic series. However, the compounds presented here display partial agonist or antagonist behavior instead of full agonist.

1. Introduction

Melatonin **1** (*N*-acetyl-5-methoxytryptamine) is a tryptophan-derived hormone characterized by a circadian rhythm of secretion[1,2] with peak levels occurring during the period of darkness. Its activity is mediated through two high-affinity G-protein coupled receptors named MT_1 and MT_2.[3,4] Whereas it is known that MT_1 and MT_2 receptors are expressed both centrally (suprachiasmatic nucleus, cortex, *pars tuberalis*, etc.) and peripherally (kidney, adipocytes, retina, blood vessels, etc.),[5] the physiological roles of these receptors are not yet fully defined. There is evidence that MT_1 receptors might be implicated in the sleep promoting effects of melatonin[6,7] and in mediating vasoconstriction in rat caudal artery,[8] whereas MT_2 receptors appear to play a major role in the resynchronizing activity of melatonin[6,9] and in mediating vasodilatation in rat caudal artery.

These last years, several series of melatonin MT_2 receptor ligands have been described (Chart 1) like indole **2**,[10] tetralin **3**[10] and benzofuran **4**.[11] Recently, **5**[12] has been reported having a binding affinity similar to melatonin at the MT_2 receptor and a good MT_2 over MT_1 selectivity ($S = 763$). The (*E*)-propenyl derivative **6**[13] was a potent MT_2 ligand, with affinities as high as melatonin, and with MT_2/MT_1 selectivity ratios higher than one hundred. The most interesting compounds belong to the N-(substituted-anilinoethyl)amide series **7**,[14] which are highly selective antagonists, with MT_2 binding affinities greater than melatonin **1**. Even if in this previous series of molecules, we reached one of our aims, that is, to obtain selective ligands, we did not obtain selective agonist for MT_2 receptor subtype. Indeed, most of the ligands were partial agonists and only two of them were full antagonists. This kind of selective MT_2 antagonist are already available and the most used in pharmacology is 4P-PDOT.[15] MT_2 receptor subtype full selective agonist are still required as a pharmacological tool. Indeed, as mentioned above the MT_2 melatonin receptor subtype is probably involved in the resynchronizing effect of melatonin. This hypothesis came from studies performed with a combination of melatonin and 4P-PDOT, a selective MT_2 antagonist.[6] The first results obtained with transgenic mice $MT_2^{-/-}$ confirmed this hypothesis. Nevertheless, when the same kind of studies was performed on $MT_1^{-/-}$, the story seems more complicated.[7,15] Therefore, selective MT_2 agonist are still needed to selectively stimulate the MT_2 receptor.

In previous studies, we reported the synthesis and the structure–selectivity relationships of a novel series of potent selective MT_2 antagonists.[16] Indeed, introduction of a phenyl substituent in the 3-position of the tetralin ring (**8** and **9**) decreased the MT_1 but maintains the MT_2 binding affinity, strongly suggesting the importance of such a phenyl substituent to achieve MT_2 selectivity.

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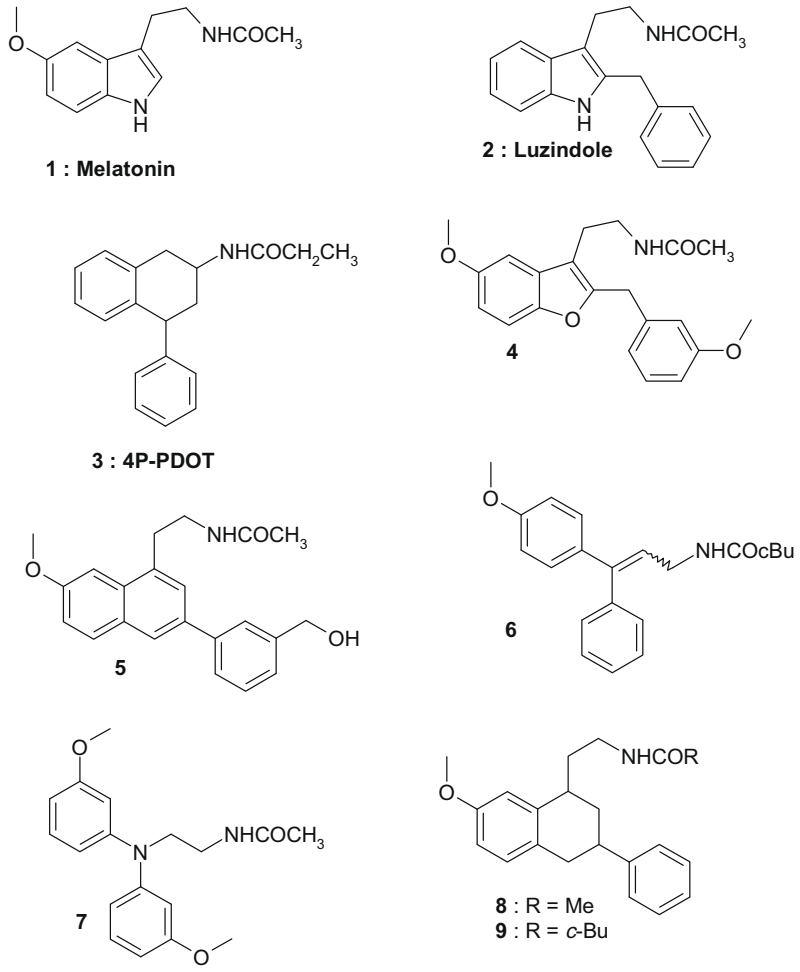


Chart 1. Chemical structures of melatonin and some representative MT_2 selective ligands.

Furthermore, when the methyl group of the acetamide was replaced the MT_1/MT_2 selectivity ratio was enhanced.

Considering the role of the phenyl substituent, the tetrahydronaphthalenic compound **8** was selected as a starting point to attempt the synthesis of highly selective MT_2 ligands of higher selectivity. The acyl group, the substitutions on the phenyl and the length of the spacer were independently modulated as reported in the present work.

We report here the synthesis and the structure–selectivity relationships of new tetrahydronaphthalenic MT_2 ligands.

2. Results and discussion

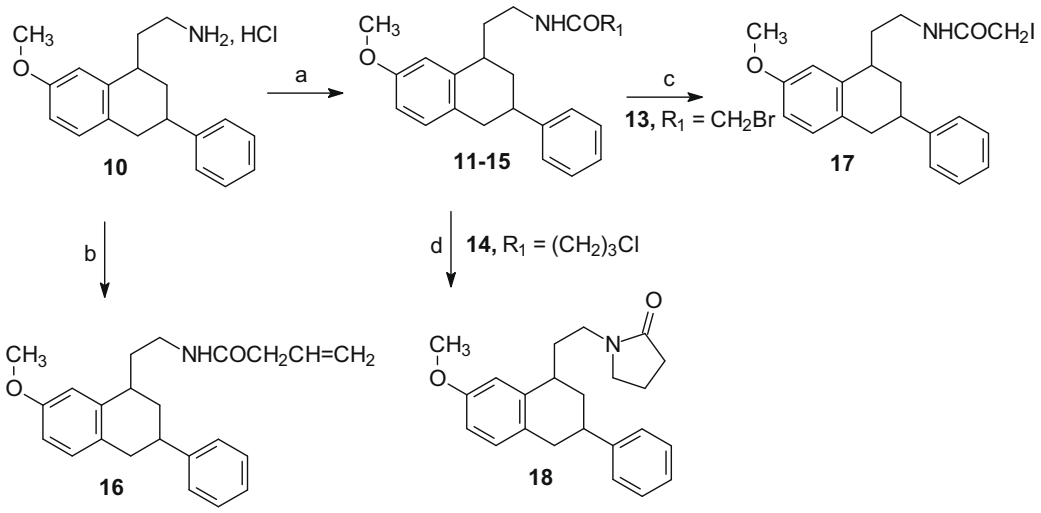
2.1. Chemistry

The synthetic pathway for compounds **11–18** is outlined in Scheme 1. Starting from 2-(7-methoxy-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethylamine hydrochloride (**10**),[15] the *N*-acyl derivatives **11–16** were obtained through two routes: (i) by treatment with the appropriate acid chlorides in the presence of K_2CO_3 as base[17] (**11–15**) and (ii) by a peptide coupling reaction type with vinylacetic acid in the presence of EDCI (**16**).

Substitution of the bromine atom of **13** with sodium iodide in acetone afforded the iodo derivative **17**. The pyrrolidinone **18** was obtained by cyclization of the chlorobutyramide **14** with EtONa in DMF. Compounds **33–35** were obtained following the synthetic route described in Scheme 2. The key tetralone intermediates **28** and **29** were synthesized from methoxybenzene according to a previously described procedure.[18] Friedel-Crafts acylation reaction gave the ketones **19–21**. Subsequently, those ketones were reacted with methyl bromoacetate in the presence of sodium hydride in DMF and the crude esters were saponified by heating in a 3 M NaOH solution to produce the acids **22–24**. Selective reduction of the ketonic group of compounds **22–24** was achieved by treatment with triethylsilane/trifluoroacetic acid[19] to afford compounds **25–27** which were cyclized to the corresponding tetralones **28** and **29** by heating in polyphosphoric acid. In these conditions, the cyclization of compound **27** afforded exclusively indanone **30**.

The tetralones **28** and **29** were cyanomethylated by a Horner-Emmons olefination[20] with diethyl cyanomethylphosphonate to give nitriles **31** and **32**. Compound **31** was hydrogenated in the presence of Raney nickel in acetic anhydride to give, after fractional recrystallization, the (±)-*cis* isomer of diacetamide **33**. The primary amine **34** was prepared from the nitrile **32** by hydrogenation in the presence of Raney nickel in a NH_3-saturated ethanol solution, and was isolated as the hydrochloride salt after treatment with gaseous HCl in ether. The amide **35** was then obtained in a biphasic medium by treatment with cyclobutanecarboxylic acid chloride in the presence of K_2CO_3.

Amide **38** was synthesized from agomelatine[21] according to the route depicted in Scheme 3. Bromination of agomelatine using bromine in acetic acid led to the 3-bromo derivative **36**.[12] This compound was coupled with 3-methoxyphenyl boronic acid under Suzuki conditions[22] in the presence of palladium acetate to afford



Scheme 1. Synthesis of compounds **11–18**. Reagents: (a) R_1COCl, K_2CO_3, $CHCl_3/H_2O$; (b) (i) NaOH, H_2O, (ii) $H_2C{=}CHCH_2COOH$, EDCI, TEA, CH_2Cl_2; (c) KI, acetone; (d) (i) EtONa, EtOH, (ii) DMF.

compound **37**. Partial reduction of the naphthalenic ring with lithium in liquid ammonia gave after fractional recrystallization the (±)-*cis* isomer of compound **38**.

The synthetic routes to the compounds bearing amidomethyl **43** or amidopropyl side chain **48** are shown in Scheme 4. Alkaline hydrolysis followed by a catalytic (Pd–C) hydrogenation of compound **39**,[14] afforded after recrystallization from ethanol, the (±)-*cis* isomer of acid **40**. Activation of the carboxylic acid function of **40** with ethyl chloroformate and subsequent reaction with sodium azide gave the azide **41**. Curtius degradation of this azide followed by acidic hydrolysis provided amine hydrochloride **42**, which was acetylated in standard conditions to afford acetamide **43**.

Esterification of acid **40** with absolute ethanol in the presence of thionyl chloride gave the ethyl ester **44**, which was converted to the cyanoethyl compound **47** via a three steps sequence: lithium aluminium hydride reduction of the ethoxycarbonyl group, mesylation of the resulting alcohol, and cyanation using potassium cyanide in DMSO. Finally, Raney nickel-catalyzed hydrogenation of **47** in acetic anhydride provided acetamide **48**.

The key intermediates in the synthetic route to 2-phenyl tetralin (**53**) and 2-benzyl tetralin (**54**) were the corresponding previously described tetralones **49**[23] and **50**[24] (Scheme 5). A Horner–Emmons reaction on these ketones using sodium hydride and diethyl cyanomethylphosphonate in anhydrous tetrahydrofuran gave nitriles 51 and 52. These nitriles were hydrogenated in the presence of Raney nickel in acetic anhydride to give, after fractional recrystallization, the (±)-*cis* isomer of the *N*-acetyl derivatives **53** and **54**.

2.2. Pharmacology

Chemical structures, binding affinities and MT_1/MT_2 selectivity ratios of the new tetralinic compounds are reported in Table 1. These compounds were evaluated for their binding affinity for membranes prepared from human MT_1 and MT_2 receptors stably transfected in Human Embryonic Kidney (HEK 293) cells or Chinese Hamster Ovarian (CHO) cells, using 2-[^{125}I]iodomelatonin as radioligand. At each receptor, binding affinities were checked for the 54 selective and non-selective newly synthesized molecules, either using the transfected HEK 293 or the CHO cell lines. The correlation between affinities in HEK 293 and CHO cells is highly significant ($r = 0.98$)[25] for both receptors. This high correlation allows the direct comparison of the affinities to draw structure–activity relationships.

The intrinsic activity of the most interesting compounds (selectivity ratio higher than 50 and K_i less than to 10 nM) has been evaluated only on the MT_2 receptor, due to their weak affinities for the MT_1 subtype. The results are shown in Table 2. The [^{35}S]-GTPγS binding assay used to determine the functional activity of the compounds was performed using Chinese Hamster Ovarian (CHO) cell lines stably expressing the human MT_2 receptors. An agonist stimulates the [^{35}S]-GTPγS binding, and this stimulation is proportional to the efficacy and intrinsic activity of the molecule. By convention, the natural ligand melatonin has an efficacy (E_{max}) of 100%. Full agonists stimulate [^{35}S]-GTPγS binding with a maximum efficacy, similar to that of melatonin. If the E_{max} is between 30% and 70%, the compound is considered as a partial agonist, whereas if it is less than 30%, the compound is considered as an antagonist. In this last case, the antagonism potency (K_B) is determined against 30 or 3 nM melatonin for MT_1 or MT_2, respectively.

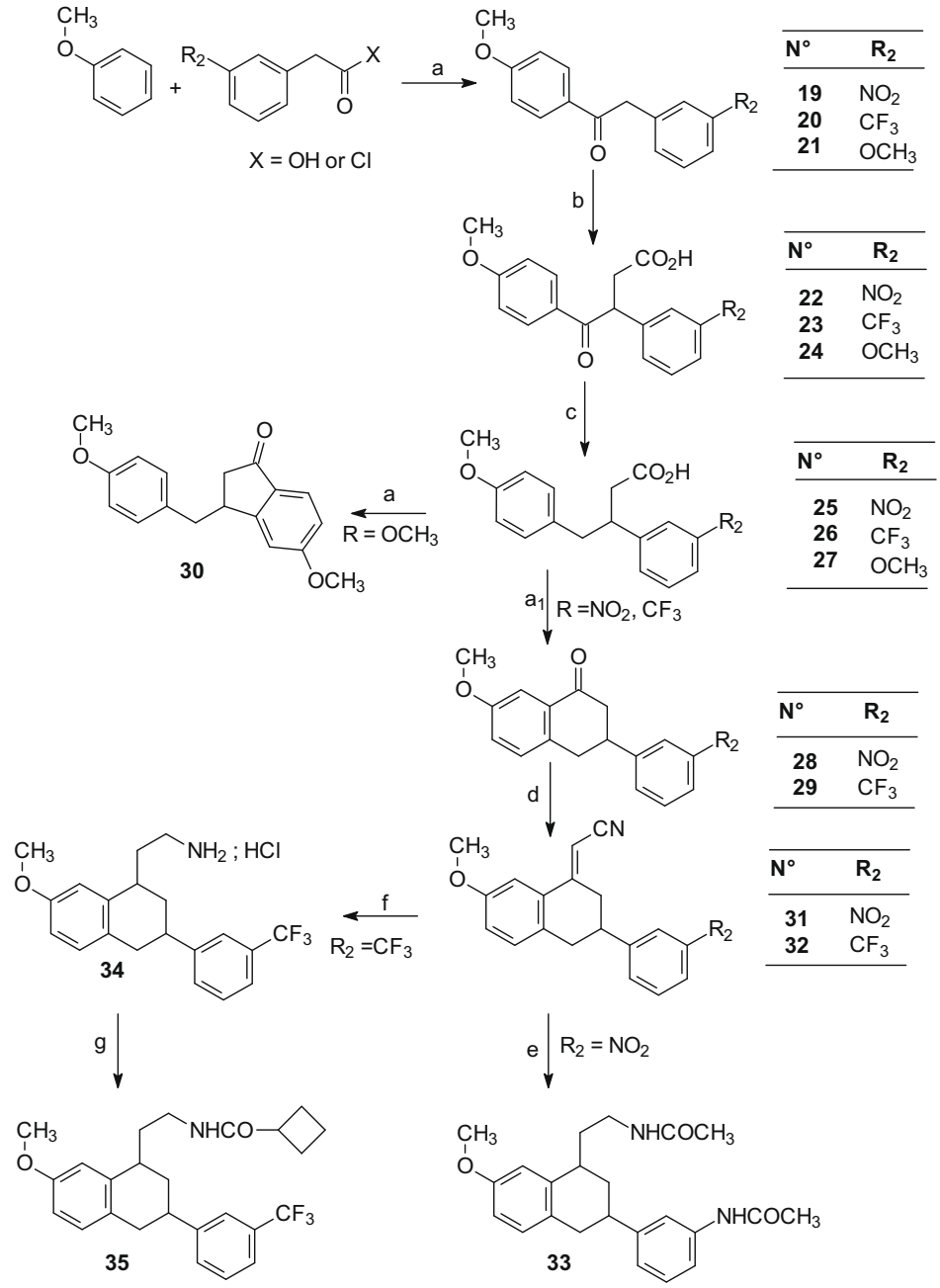
(a) *Variations of the acyl group on the C-1 side chain:*

(I) The homologation of the methyl group of **8** for ethyl (compound **11**) or propyl (compound **12**) causes a slight decrease in MT_1 affinity with a slight increase in MT_2 affinity, leading to ratios of threefold (281) and fivefold higher (350), respectively.

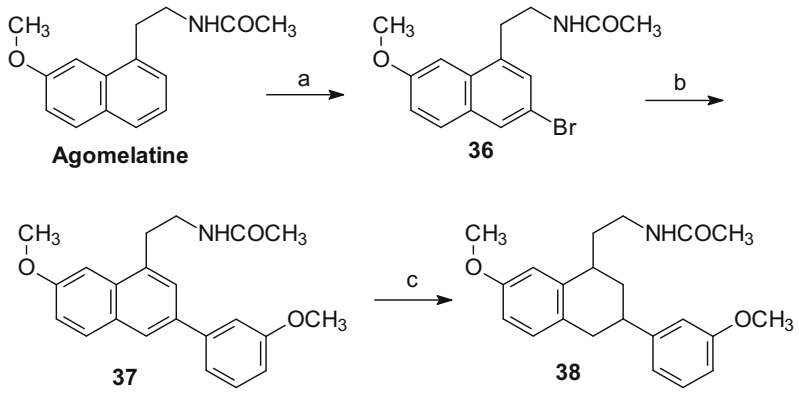
(II) The introduction of a terminal vinyl group (**15** and **16**) induces a slight decrease in selectivity by comparison with their saturated counterparts (**11** and **12**). The vinyl moiety in **15** leads to a nearly conserved MT affinities, whereas the allyl group in **16** causes a slight decrease both binding affinities.

(III) The introduction of a halogenated alkyl side chain shows the effect of a bulky group. A chloropropyl group, such as that in **14** is too bulky to achieve a good MT_2 affinity (90-fold decrease vs its non-halogenated counterpart), but its MT_1 affinity decreases by about 30 times, leading to a threefold lower selectivity. Furthermore, the iodomethyl group in **17** causes a 15-fold decrease in its MT_1 affinity and only a threefold decrease in its MT_2, resulting to a sevenfold increase in selectivity compared to **8**. A slightly smaller group, such as bromomethyl **13**, causes a sixfold increase in selectivity ($S = 426$). In fact, its MT_1 affinity is 40-fold lower than **8**, whereas its MT_2 affinity is only threefold lower.

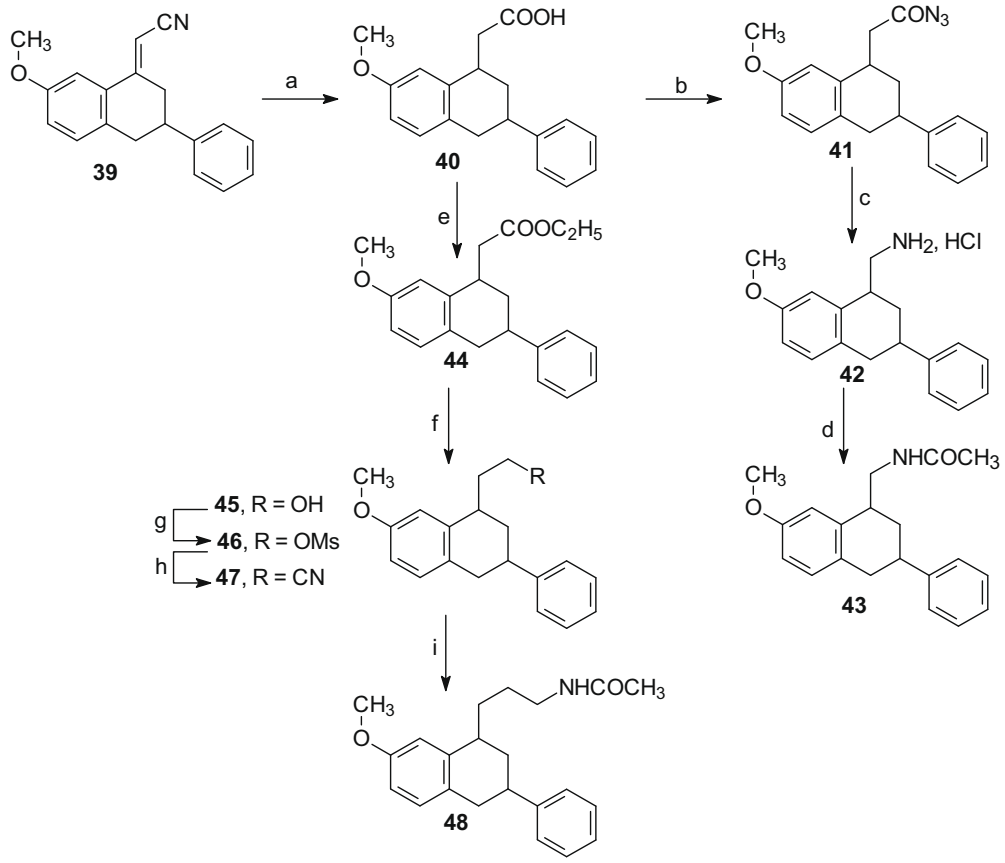
(IV) The cyclization of the amide group as in pyrolidinone **18** induces sharp decreases in MT_1 (124-fold) and MT_2 (20-fold) affinities, leading to a fivefold increase in selectivity ($S = 376$), thus suggesting that hydrogen bonding should be more important for MT_1 affinity than for MT_2.



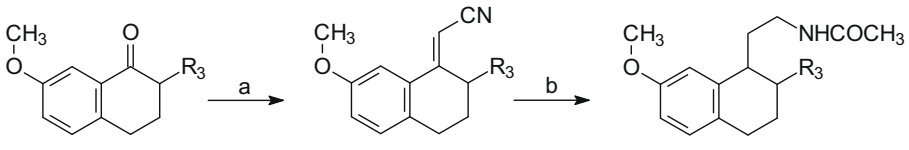
Scheme 2. Synthesis of compounds **34** and **35**. Reagents: (a) (a1) Polyphosphoric acid; (a2) $AlCl_3$, DMF; (b) (i) $BrCH_2COOCH_3$, NaH, DMF, (ii) NaOH, MeOH, water, (iii) 6 M HCl; (c) $(Et)_3SiH$, CF_3COOH; (d) $(C_2H_5O)_2P(O)CH_2CN$, NaH, THF; (e) H_2, Raney nickel, $(CH_3CO)_2O$; (f) H_2, Raney nickel, NH_3 (g), EtOH; (g) c-C_4H_7COCl, K_2CO_3, $CHCl_3/H_2O$.



Scheme 3. Synthesis of compound **38**. Reagents: (a) Br_2, AcOH; (b) 3-$OCH_3C_6H_4B(OH)_2$; (c) Li, NH_3.



Scheme 4. Synthesis of compounds **43**, **44**. Reagents: (a) (i) NaOH, MeOH, H_2O, (ii) 6 M HCl, (iii) H_2, Pd–C, EtOH; (b) (i) ClCOOEt, $N(Et)_3$, acetone, (ii) NaN_3, H_2O; (c) (i) Toluene, reflux, (ii) 6 M HCl; (d) CH_3COCl, K_2CO_3, $CHCl_3/H_2O$; (e) $SOCl_2$, EtOH; (f) $LiAlH_4$, THF; (g) CH_3SO_2Cl, $N(Et)_3$, CH_2Cl_2; (h) KCN, DMSO; (i) H_2, Raney nickel, $(CH_3CO)_2O$.



N°	R_3
49	C_6H_5
50	$CH_2C_6H_5$

N°	R_3
51	C_6H_5
52	$CH_2C_6H_5$

N°	R_3
53	C_6H_5
54	$CH_2C_6H_5$

Scheme 5. Synthesis of compounds **53**, **54**. Reagents: (a) $(C_2H_5O)_2P(O)CH_2CN$, NaH, THF; (b) H_2, Raney nickel, $(CH_3CO)_2O$.

(b) *Substitutions of the phenyl in position 3*

Previously reported results on benzofuran series[11] led us to consider various *meta-substitutions* of the phenyl in position 3. Adding a methoxy group (**38**) leads to a fourfold increase in selectivity, by decreasing 10-fold the MT_1 affinity, whereas the MT_2 affinity is only doubled. On the contrary, a trifluoromethyl group (**35**) causes a threefold decrease in MT_2 affinity versus the unsubstituted phenyl, **9**, but a sixfold increase in MT_1 affinity, resulting in a 20-fold decrease in selectivity.

(c) *Length of the spacer*

The number of carbon atoms between the tetralin and the amide has been modified. With 1 carbon in between compound **43**, there is a slight increase in MT_1 affinity, but MT_2 affinity is decreased. This gives a fourfold lower selectivity than **8**. With 3 carbons **48**, the selectivity is unchanged in respect with **8**, but the affinities for both subtypes are somewhat lower.

(d) *Substitution at 2-position of the tetralin ring*

Introduction of a phenyl (**53**) or a benzyl (**54**) group at the 2-position of the tetralin ring reduces MT_1 affinity and, to a higher extent, in the MT_2 affinity. This result confirms the importance of a phenyl substituent at the 3-postion of the tetralin ring in achieving MT_2 selectivity.

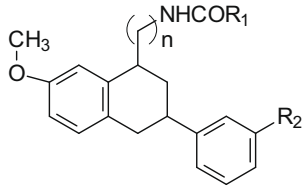
The intrinsic activities of the most interesting compounds in this report are shown in Table 2. Almost all the tested compounds act as MT_1 antagonists and as MT_2 partial agonists or antagonists.

3. Experimental

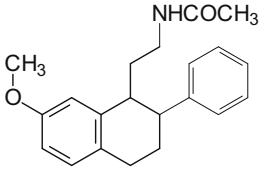
3.1. Chemistry

Melting points were determined on a Büchi SMP-20 capillary apparatus and are uncorrected. IR spectra were recorded on a Vector 22 Bruker spectrometer. ^1H NMR spectra were recorded on an AC 300 Bruker spectrometer. Chemical shifts are reported in δ units (parts

Table 1
MT_1 and MT_2 receptor binding affinities of tetralinic compounds: **11–18**, **34**, **35**, **38**, **43**, **48**



11-18, 34-35, 38, 43, 48



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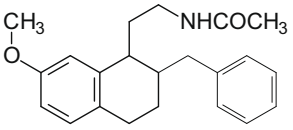

54

Compound	R_1	R_2	n	K_i ± SEM (nM) MT_1	K_i ± SEM (nM) MT_2	S MT_1/MT_2
Melatonin **1**	—	—	—	0.14 ± 0.03	0.41 ± 0.04	0.34
4P-PDOT **3**	—	—	—	108 ± 15	0.96 ± 0.23	112
8	CH_3	H	2	20.5 ± 8.70	0.31 ± 0.094	66
9	c-C_4H_7	H	2	439 ± 124	2.23 ± 0.5	191
11	C_2H_5	H	2	45 ± 6	0.16 ± 0.05	281
12	n-C_3H_7	H	2	35 ± 3	0.10 ± 0.01	350
13	CH_2Br	H	2	809 ± 232	1.9 ± 0.2	426
14	C_3H_6Cl	H	2	981 ± 50	8.9 ± 1.5	110
15	$CH{=}CH_2$	H	2	33 ± 2	0.15 ± 0.02	220
16	$CH_2CH{=}CH_2$	H	2	127 ± 31	0.66 ± 0.17	192
17	CH_2I	H	2	311 ± 45	1.04 ± 0.31	299
18	$NHCOR_1$=pyrrolidinone	H	2	2480 ± 435	6.6 ± 0.8	376
34	CH_3	$NHCOCH_3$	2	>1000	71 ± 27	>141
35	c-C_4H_7	CF_3	2	61 ± 5	6.0 ± 0.5	10
38	CH_3	OCH_3	2	247 ± 30	0.89 ± 0.13	278
43	CH_3	H	1	13 ± 3	0.88 ± 0.01	15
48	CH_3	H	3	51 ± 19	0.78 ± 0.18	65
53	—	—	—	>1000	173 ± 6	> 29
54	—	—	—	>1000	52 ± 25	44

Concentration–response curves were analyzed by non-linear regression comparing a one-site and a two sites analysis. All the curves were found to be monophasic with a Hill number close to unity (not shown). Binding affinities (nM) are expressed as mean K_i ± S.E.M of at least 3 independent experiments. The selectivity ratio between MT_1 and MT_2 receptors is calculated for compound.

Table 2
Activity values

Compound	MT_1			MT_2		
	EC_{50} ± SEM (nM)	E_{max} ± SEM (%)	K_B ± SEM (nM)	EC_{50} ± SEM (nM)	E_{max} ± SEM (%)	K_B ± SEM (nM)
Melatonin **1**	2.24 ± 0.35	110 ± 2	nd	0.49 ± 0.04	104 ± 6	nd
8[a]	Inactive	<10	126 ± 24	1.28 ± 0.39	37.4 ± 3.0	0.53 ± 0.18
9[a]	Inactive	<10	105 ± 13	Inactive	<10	2.75 ± 0.9
12	Inactive	<10	32.1 ± 11	0.41 ± 0.03	57 ± 2	>10 μM
15	Inactive	<10	43.6 ± 17.9	0.74 ± 0.03	55 ± 1	0.52 ± 0.001
18	Inactive	<10	40.6 ± 8.8	Inactive	<10	6.32 ± 0.38
38	Inactive	<10	nd	Inactive	<10	nd
43	Inactive	<10	nd	Inactive	<10	nd

Concentration–response curves were analyzed by non-linear regression. Agonist potency was expressed as EC_{50} ± S.E.M. (nM) while the maximal efficacy, E_{max} ± S.E.M. was expressed as a percentage of that observed with melatonin 1 μM (=100%). Antagonist potency to inhibit the effect of melatonin (30 or 3 nM respectively for MT_1 and MT_2 receptors) was expressed as K_B ± S.E.M. Data are mean of at least 3 independent experiments.
Inactive: no dose–response effect and nd: not determined.
[a] Ref. 16.

per million) relative to $(Me)_4Si$. Elemental analyses for final substances were performed by CNRS Laboratories (Vernaison, France). Obtained results were within ± 0.4% of the theoretical values.

For all final compounds, fractional recrystallization in adequate solvent gave the (±)-*cis* isomer. The relative configuration of the tetralinic cyclic carbons (C1 and C3) was assigned through ROESY (mixing time: 1 s). The observed cross-peaks between H1 and H3 and the lack of cross-peaks between H3 and the CH_2 of the ethyl side chain were unambiguously indicative of the *cis*-arrangement.[15]

3.2. General procedure for the preparation of amides (11–15)

Potassium carbonate (1.45 g, 10.5 mmol) was added to a solution of *cis*-2-(7-methoxy-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethylamine hydrochloride (1.1 g, 3.5 mmol), in 60 mL of water and 80 mL of chloroform. After stirring for 10 min at 0 °C, 4.0 mmol of the appropriate acid chloride was added dropwise at this temperature. The reaction mixture was stirred at room temperature for 2 h. The organic phase was separated, washed with a 1 M HCl solution and water, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the desired amide **11–15**.

3.2.1. (±)-*cis*-*N*-[2-(7-Methoxy-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl]propionamide (11)

Recrystallized from isopropyl ether; yield 43%; mp 127–129 °C; IR (neat, cm^{-1}) 3300, 1641; ^1H NMR (300 MHz, DMSO-d_6) δ 0.97 (t, J = 7.7 Hz, 3H), 1.52–1.64 (m, 2H), 2.01–2.14 (m, 4H), 2.76–2.86 (m, 3H), 2.98 (m, 1H), 3.11 (m, 2H), 3.72 (s, 3H), 6.70 (dd, J = 8.5 and

2.2 Hz, 1H), 6.84 (d, *J* = 2.2 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 7.22 (m, 1H), 7.31–7.35 (m, 4H), 7.77 (br s, 1H). Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.07; H, 8.13; N, 4.27.

3.2.2. (±)-*cis*-*N*-[2-(7-Methoxy-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl]butyramide (12)

Recrystallized from isopropyl ether; yield 41%; mp 119–121 °C; IR (neat, cm^{-1}) 3309, 1639; ^1H NMR (300 MHz, DMSO-d_6) δ 0.84 (t, *J* = 7,3 Hz, 3H), 1.55 (q, *J* = 7,3 Hz, 2H), 1.57–1.71 (m, 2H), 2.03 (t, *J* = 7,3 Hz, 2H), 2.08–2.18 (m, 2H), 2.76–2.84 (m, 3H), 2.99 (m, 1H), 3.14 (m, 2H), 3.74 (s, 3H), 6.71 (dd, *J* = 8,4 and 2,2 Hz, 1H), 6.85 (d, *J* = 2,2 Hz, 1H), 7.01 (d, *J* = 8,4 Hz, 1H), 7.23 (m, 1H), 7.20–7.27 (m, 4H), 7.83 (br s, 1H). Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.60; H, 8.32; N, 3.98. Found: C, 78.41; H, 8.44; N, 4.15.

3.2.3. (±)-*cis*-*N*-[2-(7-Methoxy-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl]bromoacetamide (13)

Recrystallized from acetonitrile; yield 38%; mp 125–126 °C; IR (neat, cm^{-1}) 3291, 1650; ^1H NMR (300 MHz, DMSO-d_6) δ *1.53–1.71* (m, 2H), 2.07–2.18 (m, 2H), 2.77–2.84 (m, 3H), 2.99 (m, 1H), 3.17 (m, 2H), 3.73 (s, 3H), 3.83 (s, 2H), 6.71 (d, *J* = 8.5 Hz, 1H), 6.85 (s, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 7.22 (m, 1H), 7.28–7.36 (m, 4H), 8.35 (br s, 1H). Anal. Calcd for $C_{21}H_{24}BrNO_2$: C, 62.69; H, 6.01; N, 3.48. Found: C, 62.61; H, 6.20; N, 3.63.

3.2.4. (±)-*cis*-4-Chloro-*N*-[2-(7-methoxy-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl] butyramide (14)

Recrystallized from acetonitrile; yield 45%; mp 114–117 °C; IR (neat, cm^{-1}) 3307, 1640; ^1H NMR (300 MHz, DMSO-d_6) δ *1.52–1.70* (m, 2H), 1.93 (m, 2H), 2.08–2.15 (m, 2H), 2.35 (t, *J* = 6,9 Hz, 2H), 2.76–2.84 (m, 3H), 3.00 (m, 1H), 3.16 (m, 2H), 3.63 (t, *J* = 6,5 Hz, 2H), 3.74 (s, 3H), 6.71 (dd, *J* = 8,1 and 2,3 Hz, 1H), 6.86 (d, *J* = 2,3 Hz, 1H), 7.00 (d, *J* = 8,1 Hz, 1H), 7.22 (m, 1H), 7.31–7.35 (m, 4H), 7.94 (br s, 1H). Anal. Calcd for $C_{23}H_{28}ClNO_2$: C, 71.58; H, 7.31; N, 3.63. Found: C, 71.55; H, 7.48; N, 3.79.

3.2.5. (±)-*cis*-*N*-[2-(7-Methoxy-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl]vinylamide (15)

Recrystallized from isopropyl ether; yield 39%; mp 96–99 °C; IR (neat, cm^{-1}) 3266, 1655; ^1H NMR (300 MHz, DMSO-d_6) δ *1.55–1.76* (m, 2H), 2.08–2.21 (m, 2H), 2.73–2.88 (m, 3H), 3.01 (m, 1H), 3.19 (m, 2H), 3.73 (s, 3H), 5.57 (dd, *J* = 9.9 and 1.9 Hz, 1H), 6.07 (dd, *J* = 17.2 and 1.9 Hz, 1H), 6.22 (dd, *J* = 17.2 and 9.9 Hz, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 6.86 (s, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 7.24 (m, 1H), 7.28–7.37 (m, 4H), 8.15 (br s, 1H). Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.76; H, 7.50; N, 4.21.

3.2.6. (±)-*cis*-*N*-[2-(7-Methoxy-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl]vinylacetamide (16)

A solution of vinylacetic acid (0.7 mL, 8.0 mmol) in 40 mL of methylene chloride was stirred at −10 °C for 20 min. Then, triethylamine (0.61 g, 6.1 mmol) and EDCI (2.1 g, 11.0 mmol) were added, and the mixture was stirred at −10 °C for 30 min. A solution of *N*-[2-(7-methoxy-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl]ethylamine (**10**) (1.60 g, 5.3 mmol) in 10 mL of methylene chloride was cooled at −10 °C and added dropwise. After 2 h of stirring at room temperature, the reaction mixture was washed with water, a 1 M HCl solution, water, a 10% NaOH solution, and water until pH 7 was reached. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was precipitated in petroleum ether and recrystallized from isopropyl ether to give 0.83 g (45% yield) of **16**; mp 127–128 °C; IR (neat, cm^{-1}) 3297, 1645; ^1H NMR (300 MHz, DMSO-d_6) δ *1.53–1.72* (m, 2H), 2.06–2.19 (m, 2H), 2.73–2.83 (m, 3H), 2.87 (d, *J* = 6.8 Hz, 2H), 2.99 (m, 1H), 3.14 (m, 2H), 3.73 (s, 3H), 5.07 (m, 2H), 5.89 (m, 1H), 6.71 (dd, *J* = 8.4 and 2.2 Hz, 1H), 6.85 (d, *J* = 2.2 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 7.23 (m, 1H), 7.28–7.37 (m, 4H), 7.89 (br s, 1H). Anal. Calcd for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01. Found: C, 78.67; H, 7.86; N, 4.17.

3.2.7. (±)-*cis*-*N*-[2-(7-Methoxy-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl]iodoacetamide (17)

A solution of compound **13** (1 g, 2.5 mmol) in 40 mL of anhydrous acetone was treated with sodium iodide (0.45 g, 3.0 mmol). The mixture was refluxed for 2 h, cooled to room temperature and filtered. Acetone was evaporated under reduced pressure and the residue was crystallized from acetonitrile to give 1.1 g (43% yield) of **17**; mp 135–138 °C; IR (neat, cm^{-1}) 3288, 1643; ^1H NMR (300 MHz, DMSO-d_6) δ 1.52–1.65 (m, 2H), 2.08–2.19 (m, 2H), 2.77–2.84 (m, 3H), 3.03 (m, 1H), 3.17 (m, 2H), 3.62 (s, 2H), 3.74 (s, 3H), 6.72 (dd, *J* = 8.3 and 2.4 Hz, 1H), 6.85 (d, *J* = 2.4 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 7.22 (m, 1H), 7.32–7.35 (m, 4H), 8.32 (br s, *J* = 5.2 Hz, 1H). Anal. Calcd for $C_{21}H_{24}INO_2$: C, 56.13; H, 5.38; N, 3.12. Found: C, 55.83; H, 5.32; N, 3.08.

3.2.8. (±)-*cis*-*N*-[2-(7-Methoxy-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl]pyrrolidin-2-one (18)

A solution of **14** (0.8 g, 2.0 mmol) in 10 mL of absolute ethanol was added dropwise to a solution of sodium (0.08 g, 3.5 gr/at) in 30 mL of absolute ethanol. The mixture was stirred at room temperature for 1 h, and then ethanol was evaporated under reduced pressure. The residue was taken off with 40 mL of dimethylformamide and refluxed for 6 h. After cooling, the mixture was hydrolyzed with water and extracted with diethyl ether. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was precipitated in petroleum ether and recrystallized from isopropyl ether to give 0.38 g (38% yield) of **18**; mp 112–115 °C; IR (neat, cm^{-1}) 1671; ^1H NMR (300 MHz, DMSO-d_6) δ *1.56–1.77* (m, 2H), 1.89 (m, 2H), 2.08–2.25 (m, 4H), 2.76–2.83 (m, 3H), 2.95 (m, 1H), 3.16 (m, 2H), 3.36 (m, 2H), 3.74 (s, 3H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.89 (s, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 7.23 (m, 1H), 7.31–7.36 (m, 4H). Anal. Calcd for $C_{23}H_{27}NO_2$: C, 79.05.13; H, 7.79; N, 4.01. Found: C, 78.67; H, 7.70; N, 4.12.

3.2.9. [1-(4-Methoxyphenyl)-2-(3-nitrophenyl]ethanone (19)

3-Nitrophenylacetic acid (27 g, 147 mmol) was added portionwise to a mixture of polyphosphoric acid (270 g) and anisole (32 mL, 294 mmol) at 70 °C. After stirring at the same temperature for 2 h, the mixture was cooled, poured into water and extracted with ether. The organic phase was washed with a 5% K_2CO_3 solution then with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a residue which was recrystallized from cyclohexane to give 39.87 g (85% yield) of **19**; mp 57–58 °C; IR (neat, cm^{-1}) 1676; ^1H NMR (300 MHz, DMSO-d_6) δ 3.85 (s, 3H), 4.58 (s, 2H), 7.08 (d, *J* = 8.9 Hz, 2H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 7.7 Hz, 1H), 8.06 (d, *J* = 8.9 Hz, 2H), 8.12 (d, *J* = 7.7 Hz, 1H), 8.18 (s, 1H).

3.2.10. [(1-(4-Methoxyphenyl)-2-(3-trifluoromethylphenyl)]ethanone (20)

3-Trifluoromethylphenyl acetyl chloride (20 g, 90.0 mmol) was added dropwise to aluminium chloride (18 g, 135 mmol) in anisole (39 g, 360 mmol). After stirring for 2 h at room temperature, the reaction mixture was poured into ice-water. The precipitate was filtered and recrystallized from cyclohexane, affording 26.5 g (70% yield) of **20**; mp 94–96 °C; IR (neat, cm^{-1}) 1665; ^1H NMR (300 MHz, DMSO-d_6) δ 3.86 (s, 3H), 4.51 (s, 2H), 7.08 (d, *J* = 9.0 Hz, 2H), 7.56–7.60 (m, 3H), 7.66 (s, 1H), 8,06 (d, *J* = 9.0 Hz, 2H).

3.2.11. [(1-(4-Methoxyphenyl)-2-(3-methoxyphenyl)]ethanone (21)

Starting from 3-methoxyphenyl acetic acid and anisole, compound **17** was obtained as colorless oil according to the procedure described for **19**. Purified by column chromatography (SiO_2, ethyl acetate/cyclohexane (1:9)); oil; yield 61%; IR (neat, cm^{-1}) 1668; ^1H NMR (300 MHz, DMSO-d_6) δ 3.76 (s, 3H), 3.85 (s, 3H), 4.31 (s, 2H), 6.77–7.00 (m, 5H), 7.25 (t, J = 7.7 Hz, 1H), 8.01 (d, J = 7.7 Hz, 2H).

3.2.12. [4-(4-Methoxyphenyl)-4-oxo-3-(3-nitrophenyl)]butyric acid (22)

NaH (60% in mineral oil) (5.2 g, 130 mmol) was added portionwise to a cooled solution of methyl bromoacetate (12.4 mL, 130 mmol) and **19** (27.1 g, 100 mmol) in dry DMF (150 mL). The reaction mixture was stirred at room temperature for 16 h and then poured into ice-water. The aqueous phase was extracted with ether and the organic layer was washed with water, aqueous potassium bicarbonate solution, and concentrated under reduced pressure. The residue was dissolved in 100 mL of methanol. After addition of 100 mL of aqueous sodium hydroxide solution (20 g, 0.5 mol), the mixture was refluxed for 1 h and then extracted twice with diethyl ether. The aqueous phase was acidified with 6 M HCl and the precipitate was filtered and recrystallized from toluene to give 16.8 g (51% yield) of **22**; mp 143–146 °C; IR (neat, cm^{-1}) 3065–2840, 1704, 1668; ^1H NMR (DMSO-d_6) δ 2.69 (dd, J = 17.0 and 4.2 Hz, 1H), 3.19 (dd, J = 17.0 and 10.5 Hz, 1H), 3.80 (s, 3H), 5.42 (dd, J = 10.5 and 4.2 Hz, 1H), 7.00 (d, J = 8.5 Hz, 2H), 7.60 (t, J = 7.9 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 8.02–8.10 (m, 3H), 8.26 (s, 1H), 12.37 (br s, 1H).

3.2.13. [4-(4-Methoxyphenyl)-4-oxo-3-(3-trifluoromethylphenyl)]butyric acid (23)

Starting from **20**, compound **23** was obtained according to the procedure described for **22**. Recrystallized from cyclohexane; yield 40%; mp 86–88 °C; IR (neat, cm^{-1}) 3060–2840, 1705, 1665; ^1H NMR (DMSO-d_6) δ 2.67 (dd, J = 17.0 and 4.5 Hz, 1H), 3.19 (dd, J = 17.0 and 10.4 Hz, 1H), 3.80 (s, 3H), 5.35 (dd, J = 10.4 Hz and 4.5 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 7.50–7.60 (m, 2H), 7.66 (d, J = 7.4 Hz, 1H), 7.77 (s, 1H), 8.06 (d, J = 8.8 Hz, 2H), 12.36 (br s, 1H).

3.2.14. [4-(4-Methoxyphenyl)-4-oxo-3-(3-methoxyphenyl)]butyric acid (24)

Starting from **21**, compound **24** was obtained according to the procedure described for **22**. Recrystallized from toluene; yield 32%; mp 158–161 °C; IR (neat, cm^{-1}) 3100–2840, 1702, 1672, ^1H NMR (DMSO-d_6) δ 2.58 (dd, J = 17.2 and 4.0 Hz, 1H), 3.14 (dd, J = 17.2 and 10.6 Hz, 1H), 3.70 (s, 3H), 3.80 (s, 3H), 5.12 (dd, J = 10.6 and 4.0 Hz, 1H), 6.78 (dd, J = 7.6 and 2.0 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.94 (s, 1H), 6.99 (d, J = 8.6 Hz, 2H), 7.20 (t, J = 7.6 Hz, 1H), 8.02 (d, J = 8.6 Hz, 2H), 12.31 (br s, 1H).

3.2.15. [4-(4-Methoxyphenyl)-3-(3-nitrophenyl)]butyric acid (25)

Triethylsilane (21 mL, 132 mmol) was added dropwise to a solution of **22** (19.8 g, 60 mmol) in 80 mL of trifluoroacetic acid. The reaction mixture was stirred vigourously at room temperature for 48 h. Trifluoroacetic acid was then evaporated under reduced pressure and the residue was taken off with petroleum ether. The resulting precipitate was filtered and recrystallized from toluene to give 13.8 g (73% yield) of **25**; mp 137–139 °C; IR (neat, cm^{-1}) 3100–2850, 1704; ^1H NMR (DMSO-d_6) δ 2.64 (m, 2H), 2.88 (m, 2H), 3.45 (m, 1H), 3.68 (s, 3H), 6.78 (d, J = 8.5 Hz, 2H), 7.02 (d, J = 8.5 Hz, 2H), 7.55 (t, J = 7.6 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 8.04 (d, J = 7.6 Hz, 1H), 8.08 (s, 1H), 12.14 (br s, 1H).

3.2.16. [4-(4-Methoxyphenyl)-3-(3-trifluoromethylphenyl)]butyric acid (26)

Starting from **23**, compound **26** was obtained according to the procedure described for **25**. Recrystallized from cyclohexane; yield 87%; mp 99–101 °C; IR (neat, cm^{-1}) 3110–2850, 1700; ^1H NMR (DMSO-d_6) δ 2.56–2.67 (m, 2H), 2.77–2.92 (m, 2H), 3.38 (m, 1H), 3.69 (s, 3H), 6.79 (d, J = 8.3 Hz, 2H), 7.00 (d, J = 8.3 Hz, 2H), 7.44–7.57 (m, 4H), 12.12 (br s, 1H).

3.2.17. [4-(4-Methoxyphenyl)-3-(3-methoxyphenyl)]butyric acid (27)

Starting from **24**, compound **27** was obtained according to the procedure described for **25**. Recrystallized from toluene; yield 96%; mp 147–150 °C; IR (neat, cm^{-1}) 3100–2830, 1702; ^1H NMR (DMSO-d_6) δ 2.52 (m, 1H), 2.79–2.81 (m, 2H), 3.23 (m, 1H), 3.34 (m, 1H), 3.70 (m, 6H), 6.72–6.80 (m, 5H), 7.01 (d, J = 7.4 Hz, 2H), 7.16 (t, J = 7.4 Hz, 1H),12.01 (br s, 1H).

3.2.18. 7-Methoxy-3-(3-nitrophenyl)-3,4-dihydro-2*H*-naphthalen-1-one (28)

A mixture of **25** (9.5 g, 30 mmol) in polyphosphoric acid (95 g) was stirred at 70 °C for 4 h. The reaction mixture was poured into 200 mL of ice-water and the precipitate was filtered, washed with water and dried. Recrystallization from toluene gave 5.2 g (58% yield) of **28**; mp 123–124 °C; IR (neat, cm^{-1}) 1679; ^1H NMR (DMSO-d_6) δ 2.78 (dd, J = 16.5 and 1.7 Hz, 1H), 3.03–3.29 (m, 3H), 3.61 (m, 1H), 3.81 (s, 3H), 7.21 (dd, J = 8.3 and 2.1 Hz, 1H), 7.34–7.41 (m, 2H), 7.67 (t, J = 8.0 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.97 (m, 1H), 8.14 (dd, J = 8.0 and 1.0 Hz, 1H).

3.2.19. 7-Methoxy-3-(3-trifluoromethylphenyl)-3,4-dihydro-2*H*-naphthalen-1-one (29)

Starting from **26**, compound **29** was obtained according to the procedure described for **28**. Recrystallized from petroleum ether; yield 89%; mp 73–75 °C; IR (neat, cm^{-1}) 1675; ^1H NMR (DMSO-d_6) δ 2.77 (dd, J = 17.3 and 1.7 Hz, 1H), 3.01–3.26 (m, 3H), 3.56 (m, 1H), 3.80 (s, 3H), 7.19 (dd, J = 8.3 and 2.9 Hz, 1H), 7.34–7.38 (d, J = 8.3 Hz, 1H), 7.40 (d, J = 2.9 Hz, 1H), 7.56–7.64 (m, 2H), 7.72–7.78 (m, 2H).

3.2.20. 5-Methoxy-3-(4-methoxybenzyl)indan-1-one (30)

Starting from **27**, compound **30** was obtained according to the procedure described for **28**. Recrystallized from ethanol; yield 49%; mp 89–91 °C; IR (neat, cm^{-1}) 1693; ^1H NMR (DMSO-d_6) δ 2.29 (dd, J = 13.6 and 3.0 Hz, 1H), 2.57–2.72 (m, 2H), 3.16 (dd, J = 13.6 and 5.3 Hz, 1H), 3.60 (m, 1H), 3.73 (s, 3H), 3.85 (s, 3H), 6.86 (d, J = 8.7 Hz, 2H), 6.98 (dd, J = 8.7 and 1.1 Hz, 1H), 7.12 (d, J = 1.1 Hz, 1H), 7.17 (d, J = 8.7 Hz, 2H), 7.91 (d, J = 8.7 Hz, 1H).

3.2.21. *E*-(7-Methoxy-3-(3-nitrophenyl)-3,4-dihydro-2*H*-naphthalen-1-ylidene)acetonitrile (31)

A solution of diethyl cyanomethylphosphonate (6.3 mL, 40 mmol) in 30 mL of anhydrous THF was added dropwise to a stirred mixture of NaH (1.6 g, 40 mmol) (60% in mineral oil) and 50 mL of anhydrous THF at −10 °C under N_2. After 1 h, a solution of **28** (5.95 g, 20 mmol) in 60 mL of anhydrous THF was added dropwise and the mixture was stirred at room temperature for 16 h. The mixture was then poured into cold water and the solid was collected by filtration, washed with water, and diethyl ether. Recrystallization from ethanol gave 6.4 g (84%) of pure **31**; mp 173–174 °C; IR (neat, cm^{-1}) 2202; ^1H NMR (300 MHz, DMSO-d_6) δ 2.97–3.18 (m, 4H), 3.34 (m, 1H), 3.80 (s, 3H), 6.47 (s, 1H), 7.05 (d, J = 8.3 Hz, 1H), 7.23 (d, J = 8.3 Hz, 1H), 7.42 (s, 1H), 7.68 (t, J = 7.3 Hz, 1H), 7.91 (d, J = 7.3 Hz, 1H), 8.15 (d, J = 7.3 Hz, 1H), 8.28 (s, 1H).

3.2.22. *E*-(7-Methoxy-3-(3-trifluoromethylphenyl)-3,4-dihydro-2*H*-naphthalen-1-ylidene)acetonitrile (32)

Starting from **29**, compound **32** was obtained according to the procedure described for **31**. Recrystallized from ethanol/water (1:1); yield 62%; mp 107–108 °C; IR (neat, cm^{-1}) 2210; ^1H NMR (DMSO-d_6) δ 2.98–3.25 (m, 5H), 3.80 (s, 3H), 6.44 (s, 1H), 7.01 (dd, J = 8.3 and 2.1 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 7.40 (d, J = 2.1 Hz, 1H), 7.54–7.77 (m, 4H).

3.2.23. (±)-*cis*-*N*-(3-(4-(2-Acetylaminoethyl)-6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)phenyl) acetamide (33)

A solution of **31** (3.21 g, 10 mmol) in 100 mL of acetic anhydride was hydrogenated over Raney nickel under pressure (50 bar) at 60 °C for 12 h. After filtration and evaporation, the residue was taken off with water and extracted with ethyl acetate. The organic phase was washed with a 10% K_2CO_3 solution then with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a residue which was recrystallized from acetonitrile to give 1.67 g (44% yield) of **33**; mp 147–148 °C; IR (neat, cm^{-1}) 3296, 1661, 1631; ^1H NMR (300 MHz, DMSO-d_6) δ *1.72–1.77* (m, 2H), 1.80 (s, 3H), 2.04 (s, 3H), 2.05–2.19 (m, 2H), 2.66–2.84 (m, 3H), 2.99 (m, 1H), 3.13 (m, 2H), 3.73 (s, 3H), 6.70 (dd, J = 8.2 and 2.3 Hz, 1H), 6.85 (d, J = 2.3 Hz, 1H), 6.98–7.02 (m, 2H), 7.24 (t, J = 8.7 Hz, 1H), 7.46–7.51 (m, 2H), 7.89 (br s, 1H), 9.92 (br s, 1H). Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.41; O, 12.61. Found: C, 72.35; H, 7.38; O, 12.96.

3.2.24. (±)-*cis*-(7-Methoxy-3-(3-trifluoromethylphenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)ethylamine hydrochloride (34)

A saturated ammonia solution of **32** (3 g, 9.0 mmol) in 150 mL of ethanol was hydrogenated for 5 h over Raney nickel under pressure (60 bars) at 60 °C. After filtration and evaporation, the residual oil was dissolved in dry diethyl ether and treated with gaseous HCl. The obtained solid was filtered and recrystallized from ethyl acetate to give 1.18 g (35% yield) of **34**; mp 185–187 °C; IR (neat, cm^{-1}) 3120–2740; ^1H NMR (300 MHz, DMSO-d_6) δ *1.73–2.34* (m, 4H), 2.75–3.52 (m, 4H), 3.71 (m, 2H), 3.80 (s, 3H), 6.79 (dd, J = 8.6 and 2.0 Hz, 1H), 6.97 (d, J = 2.0 Hz, 1H), 7.08 (d, J = 8.6 Hz, 1H), 7.59–7.75 (m, 4H), 8.15–8.23 (br s, 3H).

3.2.25. (±)-*cis*-*N*-(2-(7-Methoxy-3-(3-trifluoromethylphenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl) cyclobutylcarboxamide (35)

Starting from **34**, compound **35** was obtained according to the procedure described for compounds **11–15**. Recrystallized from isopropyl ether; yield 37%; mp 115–117 °C; IR (neat, cm^{-1}) 1654; ^1H NMR ($CDCl_3$) δ *1.62–2.32* (m, 10H), 2.77–3.02 (m, 4H), 3.12 (m, 1H), 3.40 (m, 2H), 3.82 (s, 3H), 5.37 (br s, 1H), 6.73 (dd, J = 8.4 and 2.4 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 7.43–7.52 (m, 4H). Anal. Calcd for $C_{22}H_{24}F_3NO_2$: C, 67.51; H, 6.18; N, 3.58. Found: C, 67.61; H, 6.15; N, 3.35.

3.2.26. *N*-[2-(3-Bromo-7-methoxynaphthalen-1-yl)ethyl]acetamide (36)

To a solution of *N*-[2-(7-methoxynaphthalen-1-yl)ethyl] acetamide (2 g, 8.0 mmol) in 40 mL of glacial acetic acid was added dropwise at 70 °C a solution of bromine (1.6 mL, 10 mmol) in 6 mL of glacial acetic acid. After stirring for 6 h at this temperature, the mixture was cooled, poured into ice-water and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was recrystallized from toluene to give 1.90 g (73% yield) of pure **36**; mp 104–106 °C; IR (neat, cm^{-1}) 3293, 1633; ^1H NMR (300 MHz, DMSO-d_6) δ 1.83 (s, 3H), 3.12 (t, J = 8.3 Hz, 2H), 3.33 (m, 2H), 3.94 (s, 3H), 7.22 (dd, J = 9.0 and 2.4 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.63 (d, J = 2.4 Hz, 1H), 7.83 (d, J = 9.0 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H), 8.14 (br s, 1H).

3.2.27. *N*-[2-(3-(3-Methoxyphenyl)-7-methoxynaphthalen-1-yl)ethyl]acetamide (37)

A solution of **36** (1.2 g, 0.004 mol), 3-methoxyphenylboronic acid (0.61 g, 4.0 mmol), palladium acetate (0.1 g), potassium carbonate (1.0 g, 7.0 mmol) and tetrabutylammonium bromide (15 mg) in 20 mL of dioxane and 10 mL of water was refluxed for 4 h under N_2. After cooling and filtration, the filtrate was taken with ethyl acetate and washed with water. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was recrystallized from toluene to give 0.92 g (71% yield) of pure **37**; mp 94–96 °C; IR (neat, cm^{-1}); ^1H NMR (300 MHz, DMSO-d_6) δ 1.85 (s, 3H), 3.22 (t, J = 7.4 Hz, 2H), 3.40 (m, 2H), 3.86 (s, 3H), 3.97 (s, 3H), 6.95 (dd, J = 8.8 and 1.7 Hz, 1H), 7.21 (dd, J = 8.8 and 1.7 Hz, 1H), 7.33 (d, J = 1.7 Hz, 1H),7.37–7.44 (m, 2H), 7.66 (d, J = 1.7 Hz, 1H), 7.69 (s, 1H), 7.92 (d, J = 8.8 Hz, 1H), 8.05 (s, 1H),8.17 (br s, 1H).

3.2.28. (±)-*cis*-*N*-(2-(7-Methoxy-3-(3-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl) acetamide (38)

Liquid ammonia (100 mL) was added at −33 °C to a solution of **37** (1 g, 3.0 mmol) in 50 mL of anhydrous THF under Ar. Lithium (0.2 g, 3.0 mmol) was then added portionwise and the mixture was stirred vigorously at the same temperature until the gray color of the solution has completely disappeared. A saturated aqueous solution of ammonium chloride was added dropwise then the mixture was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure, affording a residue which was crystallized from isopropyl ether to give 0.21 g (21% yield) of **38**; mp 107–109 °C; IR (neat, cm^{-1}) 3303, 1633; ^1H NMR (300 MHz, DMSO-d_6) δ *1.57–1.72* (m, 2H), 1.80 (s, 3H), 2.05–2.18 (m, 2H), 2.76–2.83 (m, 3H), 3.01 (m, 1H), 3.10–3.20 (m, 2H), 3.74 (s, 3H), 3.76 (s, 3H), 6.71 (dd, J = 8.5 and 2.4 Hz, 1H), 6.80 (dd, J = 8.0 and 2.4 Hz, 1H), 6.85 (d, J = 2.4 Hz, 1H), 6.88–6.93 (m, 2H), 7.00 (d, J = 8.5 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 7.90 (br s, 1H). Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.51; H, 7.79; N, 3.98.

3.2.29. (±)-*cis*-((7-Methoxy-3-phenyl)-1,2,3,4-tetrahydronaphthalen-1-yl) acetic acid (40)

A mixture of compound **39** (4 g, 145 mmol) in 60 mL of methanol and 60 mL of an aqueous sodium hydroxide solution (23.2 g, 580 mmol) was refluxed for 4 days. The mixture was then poured into cold water and washed with ether. The aqueous phase was acidified with concentrated HCl, afforded a precipitate which was filtered, dissolved in 150 mL of ethanol and hydrogenated over 10% palladium charcoal (0.5 g) under pressure (50 bars) at room temperature for 12 h. After filtration and evaporation, the residue was recrystallized from ethanol to give 2.41 g (56% yield) of **40**; mp 141–142 °C; IR (neat, cm^{-1}) 3250–2550, 1702; ^1H NMR (300 MHz, DMSO-d_6) δ 1.77 (m, 1H), 2.36 (m,1H), 2.56 (dd, J = 15.7 and 9.4 Hz, 1H), 2.88–3.02 (m, 3H), 3.09 (dd, J = 15.7 and 4.3 Hz, 1H), 3.52 (m, 1H), 3.81 (s, 3H), 6.77 (dd, J = 8.5 and 2.4 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 7.24–7.40 (m, 5H), 12.00 (br s, 1H).

3.2.30. (±)-*cis*-(7-Methoxy-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)acetylazide (41)

Triethylamine (2 mL, 15 mmol) and ethyl chloroformate (1.5 mL, 15.0 mmol) were added at 0 °C to a stirred solution of acid **40** (3 g, 10.0 mmol) in 50 mL of acetone. After 1 h of stirring at 0 °C, sodium azide (0.98 g, 15.0 mmol) dissolved in 1 mL of water was added, then the mixture was stirred at room temperature for 1 h, poured into water and extracted with methylene chloride. The or-

ganic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure and without heating. The residue was precipitated from petroleum ether and filtered to give 2.51 g (77% yield) of **41**; mp 46–47 °C; IR (neat, cm^{-1}) 2258, 1610; ^1H NMR (300 MHz, DMSO-d_6) δ 1.88 (m, 1H), 2.29 (m, 1H), 2.87–3.04 (m, 3H), 3.27–3.31 (m, 1H), 3.62 (dd, J = 13.1 and 6.2 Hz, 1H), 3.70 (dd, J = 13.1 and 3.8 Hz, 1H), 3.83 (s, 3H), 6.79 (dd, J = 8.3 and 2.8 Hz, 1H), 6.82 (d, J = 2.8 Hz, 1H), 7.08 (d, J = 8.3 Hz, 1H), 7.22–7.40 (m, 5H).

3.2.31. (±)-*cis*-(7-Methoxy-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)methylamine hydrochloride (42)

A solution of **41** (2.5 g, 8.0 mmol) in 30 mL of anhydrous toluene was refluxed until nitrogen was completely liberated. After evaporation, the residue was taken off with 50 mL of 6 M HCl and refluxed for 5 h. The mixture was evaporated under reduced pressure and the residue was taken off with acetonitrile. The precipitate was filtered and recrystallized from acetonitrile/methanol, 9:1, affording 2.36 g (38% yield) of **32**; mp 262–263 °C; IR (neat, cm^{-1}) 3150–2750; ^1H NMR (300 MHz, DMSO-d_6) δ 1.75 (m, 1H), 2.25 (m, 1H), 2.82–2.90 (m, 4H), 2.95 (m, 1H), 3.51 (m, 1H), 3.78 (s, 3H), 6.78 (d, J = 8.3 Hz, 1H), 6.95 (s, 1H), 7.07 (d, J = 8.3 Hz, 1H), 7.25 (m, 1H), 7.31–7.40 (m, 4H), 8.12–8.23 (br s, 3H).

3.2.32. (±)-*cis*-*N*-(7-Methoxy-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)methylacetamide (43)

Starting from **42** and acetyl chloride, compound **43** was obtained according to the procedure previously described for compounds (**11–15**). Recrystallized from isopropyl ether; yield 42%; mp 137–139 °C; IR (neat, cm^{-1}) 3270, 1639; ^1H NMR (DMSO-d_6) δ 1.62 (m, 1H), 1.80 (s, 3H), 2.11 (m, 1H), 2.79–2.88 (m, 3H), 3.07 (m, 1H), 3.19 (m, 1H), 3.67 (m, 1H), 3.74 (s, 3H), 6.74 (dd, J = 8.4 and 2.4 Hz, 1H), 6.90 (d, J = 2.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 7.23 (m, 1H), 7.30–7.38 (m, 4H), 7.89–7.95 (br s, 1H). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.71; H, 7.59; N, 4.30.

3.2.33. (±)-*cis*-(7-Methoxy-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethylacetate (44)

Thionyl chloride (15.1 mL, 208 mmol) was added dropwise at −10 °C to a stirred solution of acid **40** (3 g, 10 mmol) in 100 mL of absolute ethanol. After 12 h of stirring at room temperature, the reaction mixture was evaporated. The residue was taken off with ether, washed twice with a 10% aqueous potassium carbonate solution, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was precipitated from petroleum ether, filtered and recrystallized from ethanol to give 1.44 g (44% yield) of **44**; mp 77–78 °C; IR (neat, cm^{-1}) 1716; ^1H NMR (300 MHz, DMSO-d_6) δ 1.17 (t, J = 7.0 Hz, 3H), 1.74 (m, 1H), 2.11 (m,1H), 2.46 (dd, J = 15.7 and 9.2 Hz, 1H), 2.72–2.95 (m, 3H), 3.07 (dd, J = 15.7 and 4.3 Hz, 1H), 3.35 (m, 1H), 3.72 (s, 3H), 4.08 (q, J = 7.0 Hz, 2H), 6.73 (dd, J = 8.4 and 2.4 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 7.22 (m, 1H), 7.26–7.37 (m, 4H).

3.2.34. (±)-*cis*-2-(7-Methoxy-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethanol (45)

Lithium aluminium hydride (0.3 g, 9.0 mmol) was added portionwise to **44** (1.4 g, 4.0 mmol) in 30 mL of ether. After 30 min of stirring at room temperature, the reaction mixture was dropwise hydrolyzed with 3 M HCl. The precipitate was filtered and washed twice with 50 mL of ethyl acetate. The filtrate was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was precipitated from petroleum ether, filtered and recrystallized from ethanol/water, 1:1, affording 0.95 g (78% yield) of **45**; mp 78–80 °C; IR (neat, cm^{-1}) 3500–3100; ^1H NMR (300 MHz, DMSO-d_6) δ 1.60 (br s, 1H), 1.69 (m, 1H), 2.04 (m,1H), 2.26 (m, 1H), 2.49 (m, 1H), 2.82–2.95 (m, 3H), 3.31 (m, 1H), 3.85 (s, 3H), 4.11 (t, J = 7.1 Hz, 2H), 6.74 (dd, J = 8.4 and 2.4 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 7.25–7.40 (m, 5H).

3.2.35. (±)-*cis*-2-(7-Methoxy-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)methanesulfonylethanol (46)

Triethylamine (0.5 mL, 4.0 mmol), and then methane sulfonyl chloride (0.3 mL, 4.0 mmol) were added dropwise at −10 °C to **45** (0.9 g, 3.0 mmol) dissolved in 50 mL of methylene chloride. The reaction mixture was stirred for 1 h at room temperature and washed twice with 20 mL of 3 M HCl, then with water. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was precipitated from petroleum ether and filtered to afford 0.85 g (74% yield) of **46**; mp 88–89 °C; IR (neat, cm^{-1}) 1354 and 1169; ^1H NMR (300 MHz, DMSO-d_6) δ 1.68 (m, 1H), 2.08 (m,1H), 2.29 (m, 1H), 2.51 (m, 1H), 2.85–2.97 (m, 3H), 3.00 (s, 3H), 3.26 (m, 1H), 3.84 (s, 3H), 4.36 (t, J = 7.6 Hz, 2H), 6.76 (dd, J = 8.4 and 2.4 Hz, 1H), 6.87 (d, J = 2.4 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 7.24–7.29 (m, 5H).

3.2.36. (±)-*cis*-3-(7-Methoxy-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)propionitrile (47)

Potassium cyanide (0.4 g, 7.0 mmol) was added to a solution of **46** (0.8 g, 2.0 mmol) in 20 mL of dimethylsulfoxyde. After stirring at 80 °C for 1 h, the reaction mixture was poured into water and extracted with ether. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was precipitated from petroleum ether, filtered and recrystallized from ethanol/water, 2:1, affording 0.30 g (93% yield) of pure **47**; mp 89–90 °C; IR (neat, cm^{-1}) 2246; ^1H NMR (300 MHz, DMSO-d_6) δ 1.62 (m, 1H), 2.03 (m, 1H), 2.25 (m, 1H), 2.31–2.46 (m, 3H), 2.85–3.01 (m, 3H), 3.25 (m, 1H), 3.83 (s, 3H), 6.76 (dd, J = 8.2 and 2.4 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 7.27–7.35 (m, 5H).

3.2.37. (±)-*cis*-*N*-[3-(7-Methoxy-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)propyl]acetamide (48)

A solution of **47** (0.6 g, 2.0 mmol) in acetic anhydride was hydrogenated over Raney nickel (0.2 g) under pressure (50 bars) at 60 °C for 12 h. After cooling, acetic anhydride was evaporated, then the residue was taken off with water and extracted with ethyl acetate. The organic phase was washed with a 10% aqueous potassium carbonate solution and with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was recrystallized from isopropylic ether, affording 0.33 g (47% yield) of pure **48**; mp 102–104 °C; IR (neat, cm^{-1}) 3290, 1644; ^1H NMR (300 MHz, $CDCl_3$) δ *1.52–1.74* (m, 5H), 1.97 (s, 3H), 2.22 (m, 1H), 2.82–2.98 (m, 3H), 3.09 (m, 1H), 3.29 (m, 2H), 3.83 (s, 3H), 6.73 (dd, J = 8.4 and 2.6 Hz, 1H), 6.86 (d, J = 2.6 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 7.22–7.38 (m, 5H), 7.78 (br s, 1H). Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.02; H, 8.02; N, 4.19.

3.2.38. (7-Methoxy-2-phenyl-3,4-dihydro-2*H*-naphthalen-1-ylidene)acetonitrile (51)

Diethyl cyanomethylphosphonate (8.5 mL, 54 mmol) in 30 mL of anhydrous THF was added dropwise at −10 °C to a stirred mixture of NaH (60% in mineral oil) (2.2 g, 54 mmol) and 50 mL of anhydrous THF under N_2. After 1 h, a solution of **49** (6.8 g, 27 mmol) in 60 mL of anhydrous THF was added dropwise and the mixture was stirred at room temperature for 16 h. The mixture was then poured into ice-water and extracted with diethyl ether. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a oily residue which was purified by column chromatography (SiO_2, cyclohexane/acetone (9.5/0.5)), affording 2.2 g (30% yield) of pure **51**; mp 107–109 °C; IR (neat,

cm^{-1}) 2215; ^1H NMR (300 MHz, DMSO-d_6) δ *2.10–2.70* (m, 4H), 3.83 (s, 3H), 4.45 (m, 1H), 6.60 (s, 1H), 7.01 (dd, J = 8.5 and 2.5 Hz, 1H), 7.01–7.15 (m, 3H), 7.20–7.33 (m, 3H), 7.48 (d, J = 2.5 Hz, 1H).

3.2.39. (7-Methoxy-2-benzyl-3,4-dihydro-2*H*-naphthalen-1-ylidene)acetonitrile (52)

Starting from **50**, compound **52** was obtained according to the procedure described for **51**; yield 59%; mp 112–113 °C; IR (neat, cm^{-1}) 2212; ^1H NMR (300 MHz, DMSO-d_6) δ *1.74–1.76* (m, 2H), 2.61–2.79 (m, 3H), 3.02 (m, 1H), 3.31 (m, 1H), 3.79 (s, 3H), 6.30 (s, 1H), 7.02 (dd, J = 8.6 and 2.5 Hz, 1H), 7.16–7.34 (m, 7H).

3.2.40. (±)-*cis*-*N*-(7-Methoxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethylacetamide (53)

Starting from **51**, compound **53** was obtained according to the procedure described for **48**. Recrystallized from isopropyl ether; yield 76%; mp 126–128 °C; IR 1648 (neat, cm^{-1}); ^1H NMR (300 MHz, DMSO-d_6) δ *1.30–1.41* (m, 2H), 1.68 (s, 3H), 1.95 (m, 1H), 2.12 (m, 1H), 2.71–2.93 (m, 5H), 3.13 (m, 1H), 3.74 (s, 3H), 6.74–6.78 (m, 2H), 7.09 (d, J = 9.0 Hz, 1H), 7.19–7.26 (m, 3H), 7.30–7.36 (m, 2H), 7.67 (br s, 1H). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.99; H, 7.79; N, 4.33. Found: C, 77.79; H, 7.57; N, 4.42.

3.2.41. (±)-*cis*-*N*-(7-Methoxy-2-benzyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethylacetamide (54)

Starting from **52**, compound **53** was obtained according to the procedure described for **48**. Recrystallized from isopropyl ether; yield 25%; mp 74–75 °C; IR (neat, cm^{-1}) 1650; ^1H NMR (300 MHz, DMSO-d_6) δ 1.36 (m, 1H), 1.54–1.68 (m, 2H), 1.79 (s, 3H), 1.86 (m, 1H), 2.01 (m, 1H), 2.45–2.83 (m, 5H), 3.08 (m, 2H), 3.69 (s, 3H), 6.66–6.71 (m, 2H), 7.91 (d, J = 9.1 Hz, 1H), 7.16–7.32 (m, 5H), 7.87 (br s, 1H). Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.49; H, 7.98; N, 4.22.

3.3. Pharmacology

3.3.1. Reagents and chemicals

2-[^{125}I]Iodomelatonin (2200 Ci/mmol) was purchased from NEN (Boston, MA). Other drugs and chemicals were purchased from Sigma–Aldrich (Saint Quentin, France).

3.3.2. Cell culture

HEK (provided by A.D. Strosberg, Paris, France) and CHO cell lines stably expressing the human melatonin MT_1 or MT_2 receptors were grown in DMEM medium supplemented with 10% fetal calf serum, 2 mM glutamine, 100 IU/mL penicillin and 100 μg/ml streptomycin. Grown at confluence at 37 °C (95%O_2/5%CO_2), they were harvested in PBS containing EDTA 2 mM and centrifuged at 1000*g* for 5 min (4 °C). The resulting pellet was suspended in Tris 5 mM (pH 7.5), containing EDTA 2 mM and homogenized using a Kinematica polytron. The homogenate was then centrifuged (95,00*g*, 30 min, 4 °C) and the resulting pellet suspended in 75 mM Tris (pH 7.5), 12.5 mM $MgCl_2$ and 2 mM EDTA. Aliquots of membrane preparations were stored at −80 °C until use.

3.3.3. Binding asays

2-[^{125}II]Iodomelatonin binding assay conditions were essentially as previously described.[25] Briefly, binding was initiated by addition of membrane preparations from stable transfected HEK or CHO cells diluted in binding buffer (50 mM Tris–Cl buffer, pH 7.4, containing 5 mM $MgCl_2$) to 2-[^{125}II]iodomelatonin (25 or 200 pM for MT_1 and MT_2 receptors, respectively, expressed in HEK cells or 20 pM for MT_1 and MT_2 receptors expressed in CHO cells) and the tested drug. Non-specific binding was defined in the presence of 1 μM melatonin. After 120 min incubation at 37 °C, reaction was stopped by rapid filtration through GF/B filters presoaked in 0.5% (v/v) polyethylenimine. Filters were washed three times with 1 mL of ice-cold 50 mM Tris–Cl buffer, pH 7.4.

Data from the dose–response curves (seven concentrations in duplicate) were analyzed using the program PRISM (Graph Pad Software Inc., San Diego, CA) to yield IC_{50} (inhibitory concentration 50). Results are expressed as $K_i = IC_{50}/1 + ([L]/K_D)$, where $[L]$ is the concentration of radioligand used in the assay and K_D, the dissociation constant of the radioligand characterizing the membrane preparation.

[^{35}S]-GTPγS binding assay was performed according to published methodology.[25] Briefly, membranes from transfected CHO cells expressing MT_2 receptor subtype and compounds were diluted in binding buffer (20 mM HEPES, pH 7.4, 100 mM NaCl, 3 μM GDP, 3 mM $MgCl_2$, and 20 μg/mL saponin). Incubation was started by the addition of 0.2 nM [^{35}S]-GTPγS to membranes (20 μg/mL) and drugs, and further followed for 1 h at room temperature. For experiments with antagonists, membranes were preincubated with both the melatonin (3 nM) and the antagonist for 30 min prior the addition of [^{35}S]-GTPγS. Non-specific binding was defined using cold GTPγS (10 μM). Reaction was stopped by rapid filtration through GF/B filters followed by three successive washes with ice-cold buffer.

Usual levels of [^{35}S]-GTPγS binding (expressed in dpm) were for CHO-MT_2 membranes: 2000 for basal activity, 8000 in the presence of melatonin 1 μM and 180 in the presence of GTPγγS 10 μM which defined the non-specific binding. Data from the dose–response curves (seven concentrations in duplicate) were analyzed by using the program PRISM (Graph Pad Software Inc., San Diego, CA) to yield EC_{50} (effective concentration 50%) and E_{max} (maximal effect) for agonists. Antagonist potencies are expressed as $K_B = IC_{50}/1 + ([Ago]/EC_{50}\ ago)$, where IC_{50} is the inhibitory concentration of antagonist that gives 50% inhibition of [^{35}S]-GTPγS binding in the presence of a fixed concentration of melatonin ([Ago]) and EC_{50} ago is the EC_{50} of the molecule when tested alone. I_{max} (maximal inhibitory effect) was expressed as a percentage of that observed with melatonin at 3 nM for MT_2 receptor.

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