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Design, synthesis and pharmacological evaluation of novel naphthalenic derivatives as selective MT_1 melatoninergic ligands

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ABSTRACT

Novel heterodimer analogues of melatonin were synthesized, when agomelatine (**1**) and various aryl units are linked via a linear alkyl chain through the methoxy group. The compounds were tested for their actions at melatonin receptors. Several of these ligands are MT_1-selective with nanomolar or subnanomolar affinity. In addition, while most of the derivatives behave as partial agonists on one or both receptor subtypes, *N*-[2-(7-{4-[6-(1-methoxycarbonylethyl)naphthalen-2-yloxy]butoxy}naphthalen-1-yl)ethyl]acetamide (**36**), a subnanomolar MT_1 ligand with an 11-fold preference over MT_2 receptors, is a full antagonist on both receptors. Our results also confirm that the selectivity seen for the MT_1 receptor arises predominantly from steric factors and is not a consequence of the bridging of melatonin receptor dimers.

1. Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine, MLT[a], Chart 1)[1] is a neurohormone synthesized and secreted by the pineal gland following a circadian rhythm, with peak levels occurring at night. This hormone plays a role in a myriad of physiological functions including, in mammals, the control of seasonal reproduction,[2] circadian adjustments,[3] immunoresponsiveness,[4] vascular regulation,[5] and cancer growth inhibition.[6] Nevertheless, clinical trials have only confirmed the resynchronizing effects of melatonin, which might be of interest in the regulation of disrupted circadian rhythms and sleep disorders. The diversity of melatonin response within the body may be attributed to the fact that its receptors are expressed in the central nervous system and in a wide variety of peripheral tissues.[7–11]

In mammals, MLT activates two high affinity G-protein-coupled cell-membrane receptors, MT_1 and MT_2, which were cloned in the mid-1990s.[2,3,7,8] Moreover, another MLT binding site with a lower affinity profile, denoted MT_3,[12] has been characterized as a melatonin-sensitive form of the human enzyme quinone reductase 2.[13,14]

Recently, several selective MT_2[15–27] and MT_3,[28] receptor ligands have been described as competitive agonists or antagonists with varying degrees of selectivity. Several antagonists such as luzindole,[29] the first MT_2 receptor competitive antagonist discovered, and 4P-PDOT (4-phenyl-2-propionamidotetralin),[30] allowed for the identification of several physiological responses mediated by MLT receptors. The former demonstrated the role of MT_2 receptors in mediating inhibition of dopamine release in rabbit retina, while both compounds blocked melatonin-mediated phase advances of circadian rhythms in mice.[3]

However, elucidation of the pathophysiological function of the MT_1 receptor has been hampered mainly by the limited availability of selective full agonist and/or full antagonist for this receptor subtype. Consequently, synthesis and design of selective MT_1 receptor ligands with better affinity and selectivity may aid in the assessment and characterization of the role of this receptor.

A few examples of selective MT_1 receptor ligands have been reported in the literature. One of the first selective MT_1 ligand described, **2** (S24268, Chart 1)[31] consists of two *N*-(2-(naphthalen-1-yl)ethyl)acetamide moieties, or desmethoxy agomelatine, dimerized at the 6-position of the aromatic ring ($MT_2/MT_1 = 70$). Constitutive homo (MT_1–MT_1 or MT_2–MT_2) and hetero-dimerization (MT_2–MT_1) among high affinity melatonin receptors were observed in Human Embryonic Kidney (HEK 293) cells and it was

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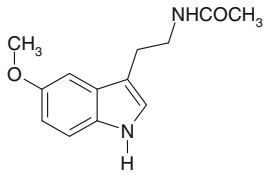
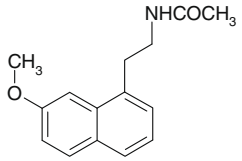
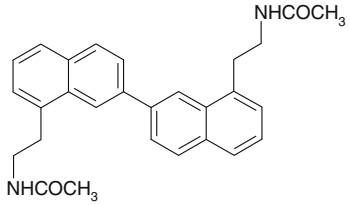


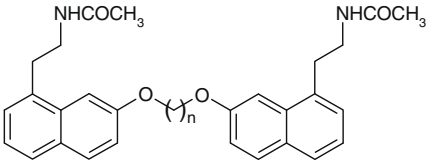
Melatonin (MLT)



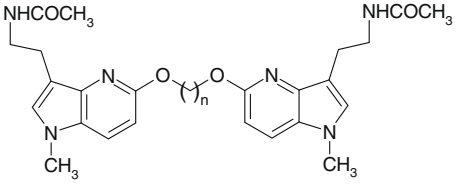
1, **Agomelatine**



2, (S24268)



3, n= 3 ; **4**, n = 4



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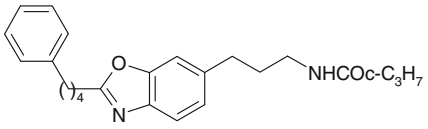
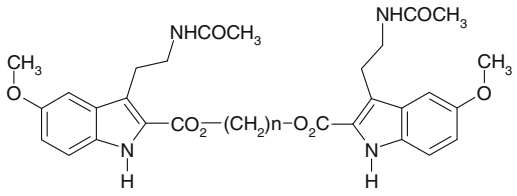


6, Benzoxazole derivative



7, Melatonin Dimers

Chart 1. Chemical structures of melatonin, agomelatine and several representative MT_1-selective ligands.

demonstrated that MT_1 homodimers and MT_2–MT_1 heterodimers represent the majority of all complexes.[32,33]

In light of the structural framework of these receptors, a series of agomelatine dimers (**3**, **4**, Chart 1)[34] was synthesized in our laboratory in accordance with the 'bivalent ligand' approach employed by Portoghese. The premise of this concept was that a bivalent ligand with an optimal distance between the two pharmacophores would exhibit a greater potency than that derived from the sum of its monovalent counterparts by allowing the bridging between dimeric receptors.[35] Investigation of varying lengths of the alkyl linker determined an optimal distance of 3–4 carbons between the agomelatine moieties (Chart 1, MT_2/MT_1 = 224 for compound **3** and MT_2/MT_1 = 120 for compound **4**). Since a spacer of 3–4 carbons did not attain the length required to permit a bivalent ligand to bridge neighboring receptors, it was suggested that the second pharmacophore participated in steric interactions in or near the MT_1 receptor pocket but not in or near the MT_2 receptor pocket.

An alternative possibility is that the receptors dimerise and the two recognition sites are brought close together. However, we cannot test this directly with current technology. However multiple sites exist within a single receptor which can still lead to selectivity allowing the use of dimer drugs. The molecular architecture of ligands and receptor mutation experiments reveal a three binding site hypothesis for the interaction of ligands with monoamine G-protein coupled receptors: implications for combinatorial ligand design.[36]

A series of dimers in which two azaindole pharmacophores (**5**, Chart 1)[37] were connected together through a linear alkyl chain, was later reported, but these compounds displayed lower affinity and weaker selectivity (2–20-fold) compared to our first series of dimers. Recently, novel benzoxazole derivatives (**6**, Chart 1)[38] has been reported as a highly potent human MT_1 ligand with moderate receptor selectivity (selectivity (S) = 35). New melatonin dimeric derivatives (**7**, Chart 1)[39] with two melatonin units linked together with a polymethylene spacer through the MLT acetamide function or through a C-2 carboxyalkyl group were also described. However, they did not show significant MT_1 selectivity. In this study, we present a novel series of MT_1-selective compounds based on our previous work on agomelatine dimers.

Compound **4** a symmetric dimer bearing a four carbons alkyl spacer, was chosen as a template and modified by altering one of its agomelatine moieties, generating a series of novel asymmetric heterodimers.

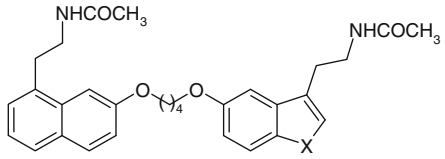
2. Chemistry

Key intermediates in the synthesis of the target compounds **15**, **16**, **18** and **19** (Table 1) are the corresponding hydroxy derivatives **8b**–**11b** and **13** (Scheme 1). Derivatives **8b**–**11b** were obtained from the previously described methoxy derivatives **8a**–**11a** by cleavage of the methyl ether using boron tribromide (Scheme 1).[40–44] The reaction of melatonin with benzenesulfonyl chloride in the presence of sodium hydroxide and a phase transfer catalyst provided the corresponding sulfonamide **12**.[28] Subsequent treatment of **12** with boron tribromide afforded the hydroxy compound **13**.

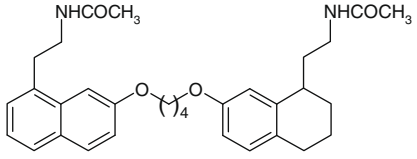
Reaction of compound **8b** with an excess of 1,4-dibromobutane in the presence of potassium carbonate in acetonitrile provided the bromobutyl analogue **14** (Scheme 2). Phenolic derivatives **9b**–**11b** and **13** were then alkylated with the bromobutyl derivative **14** in the presence of potassium carbonate in acetonitrile to give the corresponding *O*-alkylated derivatives **15**–**17** and **19** (Scheme 2). Deprotection of **17**–**18** was carried out with magnesium and ammonium chloride in methanol.[28]

Heterodimers **24**–**26** and homodimers **29**–**30** were prepared according to the synthetic pathway illustrated in Scheme 3. The first step involved the reaction of (7-hydroxynaphthalen-1-yl)ethylamine (**20**) with di-*tert*-butyldicarbonate in methylene chloride to generate the carbamate **21**. This compound was then alkylated with **14** or 1,4-dibromobutane to give compounds **22** and **27**, respectively. Removal of the Boc protecting group of these compounds was carried out with a saturated methanolic solution of

Table 1
MT_1 and MT_2 receptor binding affinities of compounds **15**–**19**

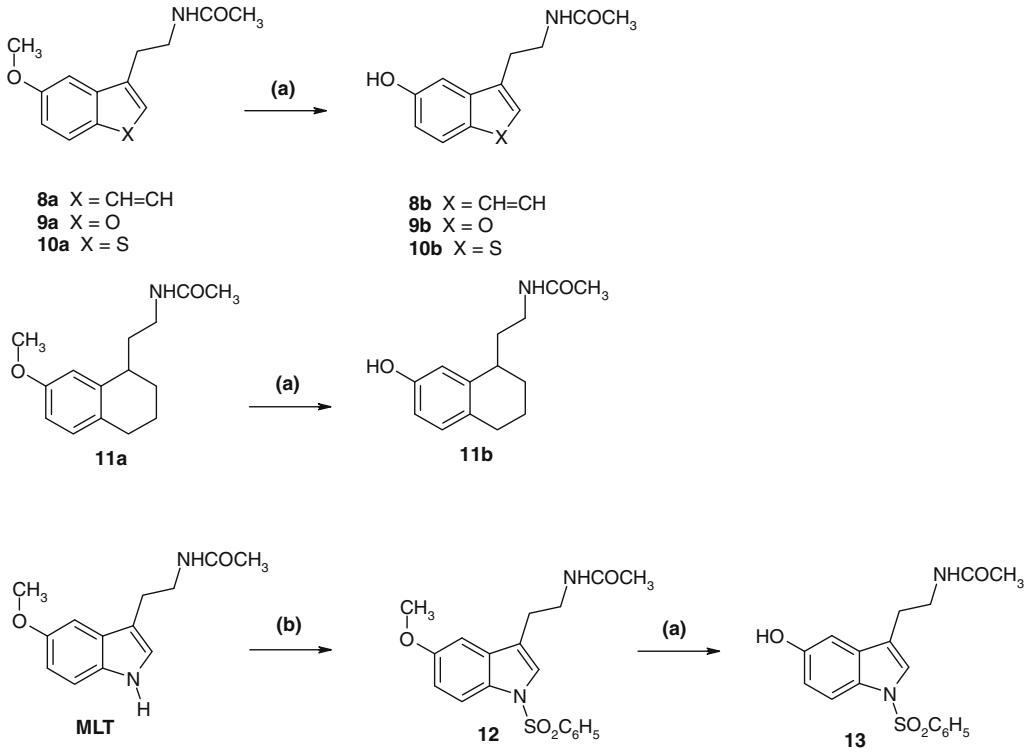


4, 15-17

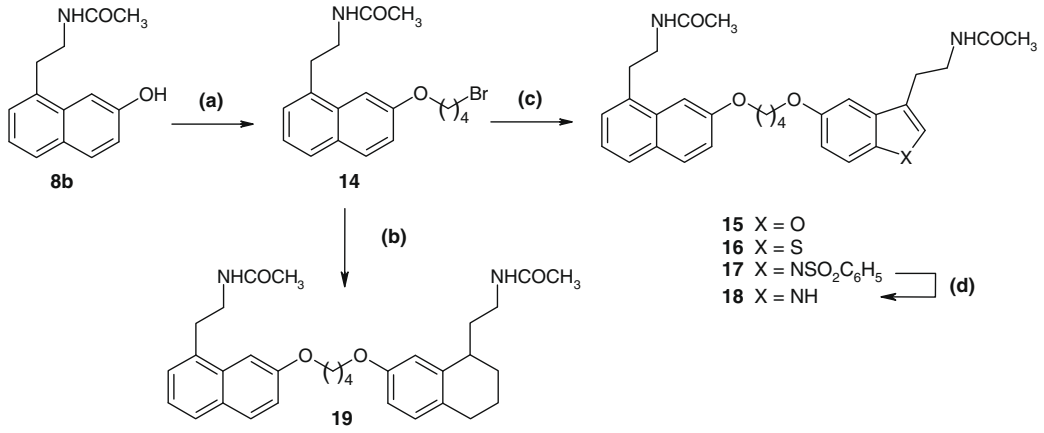


19

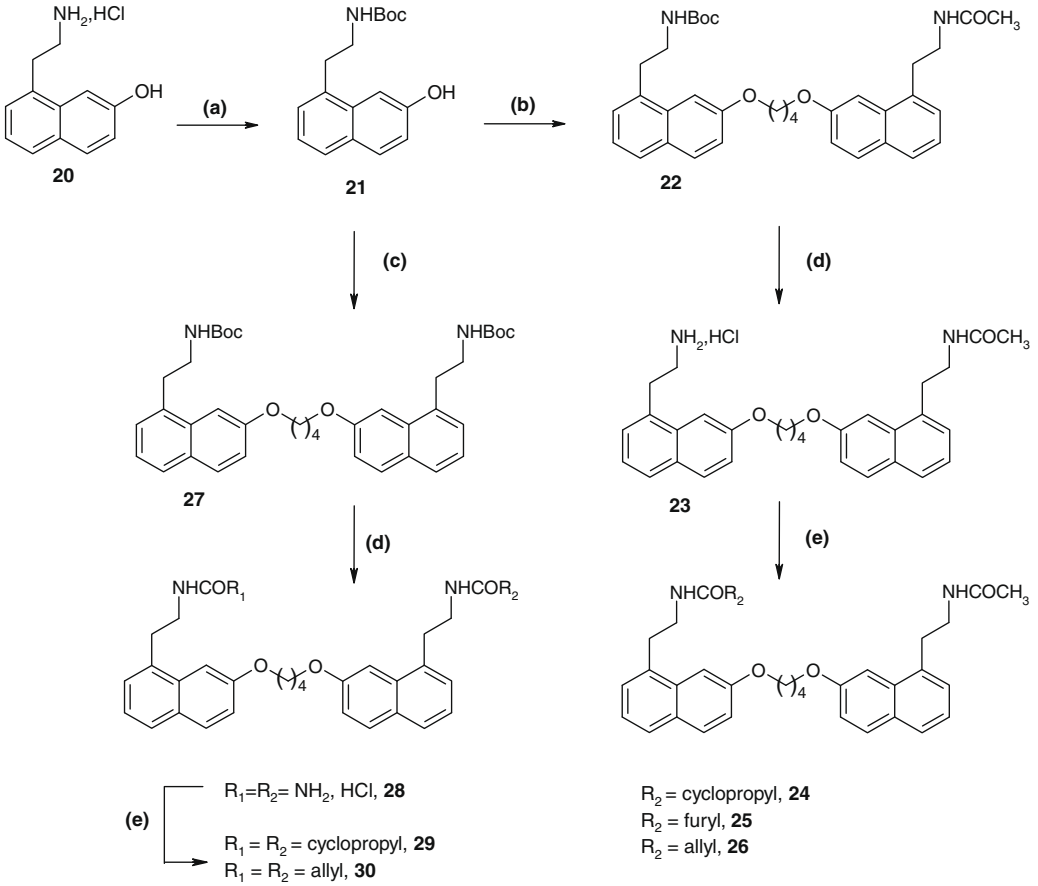
Compd	X	K_i (nM) MT_1	K_i (nM) MT_2	S (MT_2/MT_1)
4	CH=CH	0.60 ± 0.04	72.70 ± 22.20	120
15	O	1.38 ± 0.52	13.90 ± 1.85	10
16	S	3.47 ± 1.13	16.90 ± 1.90	5
18	NH	4.04 ± 0.90	84.30 ± 18.80	21
19	—	0.26 ± 0.01	6.79 ± 1.73	26



Scheme 1. Preparation of phenolic compounds: **8b**–**11b** and **13**. Reagents: (a) BBr_3, CH_2Cl_2; (b) NaOH, $(n\text{-}Bu)_4N^+NHSO_4^-$, $C_6H_5SO_2Cl$.



Scheme 2. Synthesis of compounds **15**, **16**, **18** and **19**. Reagents: (a) $Br(CH_2)_4Br$, K_2CO_3, CH_3CN, Δ; (b) **11b**, K_2CO_3, CH_3CN, Δ; (c) **9b** or **10b** or **13**, K_2CO_3, CH_3CN, Δ; (d) Mg, NH_4Cl, MeOH.

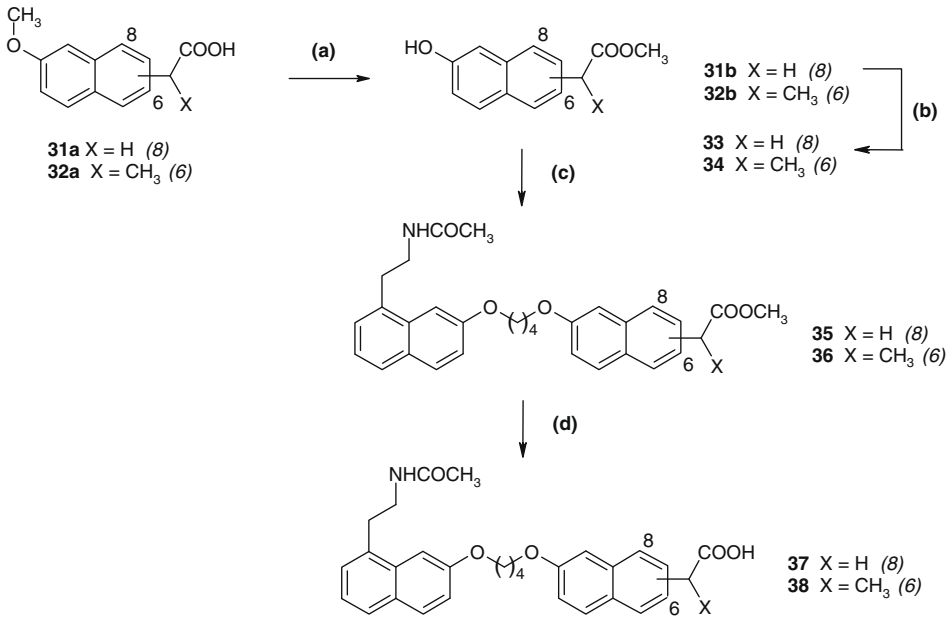


Scheme 3. Synthesis of compounds **24**–**26**, **29** and **30**. Reagents: (a) Et_3N, $(Boc)_2O$, CH_2Cl_2; (b) **14**, K_2CO_3, CH_3CN, reflux; (c) $Br(CH_2)_4Br$, K_2CO_3, CH_3CN, reflux; (d) HCl(g), MeOH; (e) RCOCl, K_2CO_3, H_2O, $CHCl_3$ for **24**, **25** and **29** or CH_2CHCH_2COOH, EDCI, CH_2Cl_2 for **26** and **30**.

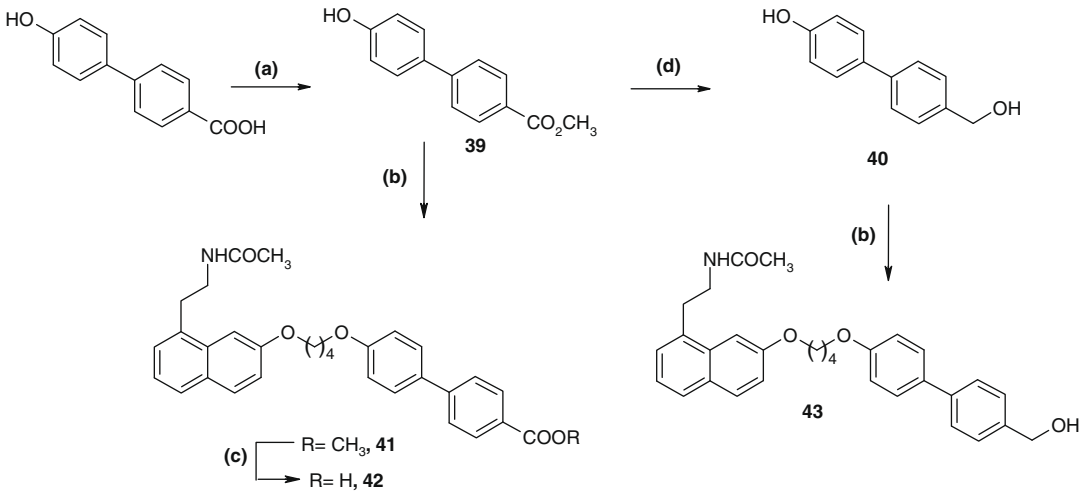
hydrochloric acid. The N-acylated compounds **24**–**26** and **29**, **30** were then prepared from amines **23** and **28** by reaction with the appropriate acyl chloride in the presence of potassium carbonate or by reaction with vinylacetic acid in the presence of EDCI.

Preparation of compounds **35–38** is reported in Scheme 4. Compounds **31b** and **32b** were easily obtained from the commercially available **31a** and **32a** by action of concentrated hydrobromic acid in refluxing acetic acid. These acids were then esterified using thionyl chloride in methanol to give compounds **33** and **34**, which were then reacted with **14** to form the respective dimers **35** and **36**. Finally, treatment of **35** and **36** with sodium hydroxide led to the heterodimers **37** and **38**.

Compounds **41**–**43** were prepared as shown in Scheme 5. 4-(4′-Hydroxyphenyl)benzoic acid was converted to the corresponding ester **39** using thionyl chloride in methanol. Alkylation of **39** with the bromobutyl derivative **14** gave dimer **41**, which was treated with sodium hydroxide to give the target acid **42**. Reduction of the ester group of **39** with lithium aluminium hydride gave the hydroxymethyl derivative **40**, which was then alkylated with compound **14** to give the target compound **43**.



Scheme 4. Synthesis of compounds **35**–**38**. Reagents: (a) HBr 47% in water, AcOH, Δ; (b) $SOCl_2$, MeOH; (c) **14**, K_2CO_3, CH_3CN, reflux; (d) NaOH, H_2O, MeOH, THF.



Scheme 5. Synthesis of compounds **41**–**43**. Reagents: (a) $SOCl_2$, MeOH; (b) **14**, K_2CO_3, CH_3CN, reflux; (c) NaOH, H_2O, MeOH, THF; (d) $LiAlH_4$, THF.

3. Pharmacology

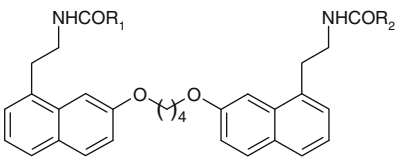
All final compounds were tested in binding studies for efficiency in human MT_1 and MT_2 receptors transfected in Chinese Hamster Ovarian (CHO[a]) cells, using 2-[^{125}I]-iodomelatonin as radioligand.[31] The [^{35}S]-GTPγS binding assay using CHO cell lines stably expressing the human MT_1 or MT_2 receptors was used to determine the functional activity of the compounds.

4. Results and discussion

The chemical structures, binding affinities and MT_2/MT_1 selectivity ratios of the new compounds are presented in Tables 1–4. The results of the evaluation of the intrinsic activity are shown in Table 5.

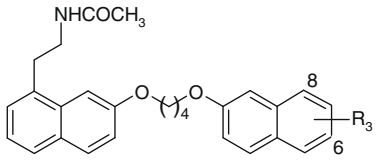
The synthesis and binding properties at MT_1 and MT_2 receptors of the first series of agomelatine dimers, in which two agomelatine moieties are linked together through their methoxy substituent by a polymethylene side chain, has been reported earlier by our

Table 2
Modulation of the *N*-acyl side chain



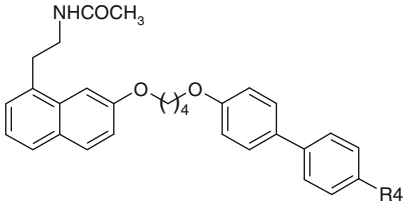
Compd	R_1	R_2	K_i (nM) MT_1	K_i (nM) MT_2	S (MT_2/MT_1)
4	CH_3	CH_3	0.60 ± 0.04	72.70 ± 22.20	120
24	CH_3	c-C_3H_5	1.07 ± 0.34	11.10 ± 2.73	10
25	CH_3	2-Furyl	0.64 ± 0.00	11.80 ± 2.81	18
26	CH_3	$CH_2CH{=}CH_2$	0.79 ± 0.22	8.45 ± 1.66	11
29	c-C_3H_5	c-C_3H_5	1.01 ± 0.23	13.6 ± 0.85	13
30	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	0.92 ± 0.26	10.9 ± 1.05	12

Table 3
Replacement of the *N*-acyl side chain by an ester or an acid group



Compd	R_3	K_i (nM) MT_1	K_i (nM) MT_2	S (MT_2/MT_1)
35	8-$CH_2CO_2CH_3$	0.07 ± 0.01	1.84 ± 0.16	26
36	6-$CH(CH_3)CO_2CH_3$	0.37 ± 0.08	4.22 ± 1.76	11
37	8-CH_2CO_2H	9.10 ± 1.11	45.80 ± 6.65	5
38	6-$CH(CH_3)CO_2H$	1.51 ± 0.42	59.10 ± 1.70	39

Table 4
Replacement of an agomelatine molecule by a biphenyl group



Compd	R_4	K_i (nM) MT_1	K_i (nM) MT_2	S (MT_2/MT_1)
41	CO_2CH_3	2.37 ± 0.89	19.10 ± 1.57	8
42	CO_2H	0.55 ± 0.01	51.30 ± 3.12	93
43	CH_2OH	0.09 ± 0.00	6.53 ± 0.07	72

group.[34] The most selective compounds contained three and four carbon spacers. The homodimer with a linker length of four carbons (**4**, MT_2/MT_1 = 120) was later predicted in silico to have a better metabolic stability than its more selective three carbon spacer homolog. In the study presented herein, we therefore decided to select compound (**4**) as a lead compound to investigate structure-affinity and structure–activity relationships for MT_1 and MT_2 receptors.

Numerous reasons exist for the use of bioisosterism in medicinal chemistry. This includes the necessity to gain selectivity for a determined receptor, modify the intrinsic activity and optimize pharmacokinetics. Bioisosteric replacement of one of the agomelatine unit of our lead compound with benzofuran, benzothiophene, and indole nuclei led to compounds **15**, **16** and **18**, which displayed higher affinities for the MT_1 receptors than for the MT_2 receptors (Table 1). However, their selectivities (MT_2/MT_1 = 10, 5, 21, respectively) remained inferior to that of the reference ligand (**4**; MT_2/MT_1 = 120). Interestingly, tetralinic analogue **19** displayed greater affinity for the MT_1 receptor (0.26 nM) than compound (**4**) and a selectivity ratio of 26.

The influence of the *N*-acylamino group of the lead compound was also examined with compounds **24**–**26**, **29** and **30** (Table 2) as it has been reported that this group plays a primary role in agonist action to MLT receptors.[41] To this end, one or both of the methyl groups of the *N*-acylamido side chains were replaced by cyclopropyl, furyl and allyl moieties. While affinity was retained for MT_1, increased affinity for MT_2 was also seen, which resulted in a loss of selectivity, the MT_2/MT_1 ratios between 10 and 18.

The *N*-acyl side chain has a primary importance for the efficacy of binding of a ligand to melatonin receptors. Removal of this feature usually results in a complete loss of affinity and is equivalent to converting a melatoninergic ligand to a non-melatoninergic ligand. A small set of analogues was synthesized with a view to probing the importance of having an *N*-acyl side chain on both units of the dimer. Replacement of one ethylacetamide group by either methyl acetate or acetic acid in position 8 and by methyl 2-propanoate or its corresponding acid in position 6 had no favorable effect on the selectivity (Table 3, compounds **35**–**38**). In this series, compound **35** presented an excellent affinity for the MT_1 receptor (0.07 nM) and an affinity of 1.84 nM for the MT_2 receptor, giving a selectivity ratio of 26. Conversion of the ester to its corresponding acid resulted in a reduced affinity for both MT_1 and MT_2 (130-fold and 25-fold, respectively). Compound **36**, bearing a methyl 2-propanoate function in position 6, showed a subnanomolar MT_1 affinity (0.37 nM) and an 11-fold selectivity over MT_2. Its hydrolysis led to reduced affinity for MT_1 and MT_2 (4-fold and

Table 5
Intrinsic activity values

Compd	MT_1				MT_2			
	K_B (nM)	I_{max} (%)	EC_{50} (nM)	E_{max} (%)	K_B (nM)	I_{max} (%)	EC_{50} (nM)	E_{max} (%)
MLT[33]	nd	nd	2.2 ± 0.4	110 ± 2	nd	nd	0.49 ± 0.04	104 ± 6
1[33]	nd	nd	1.6 ± 0.4	101 ± 6	nd	nd	0.10 ± 0.04	91 ± 7
4	11 ± 1.0	68 ± 10	73 ± 7	25 ± 1	29 ± 11	80 ± 4	405 ± 35	39 ± 3
15	27.5 ± 5.9	42.5 ± 11.5	2.49 ± 0.49	78.5 ± 18.5	160 ± 55.5	92.6 ± 3.3	$>1 \times 10^{-5}$	nd
16	5.43 ± 2.3	46 ± 14	1.94 ± 0.62	55.5 ± 0.5	60.8 ± 25	39.5 ± 7.5	20.6 ± 11.9	45.7 ± 7.36
18	10.6 ± 6.0	48.5 ± 4.5	2.38 ± 1.02	79 ± 22.7	300 ± 143	111.7 ± 14	$>1 \times 10^{-5}$	nd
19	6.24 ± 2	68.5 ± 3.5	7.75 ± 71.9	32.7 ± 9.9	122 ± 36	105.5 ± 7.5	$>1 \times 10^{-5}$	nd
24	5.2 ± 1.1	75 ± 5.1	9.1 ± 4.3	27.3 ± 2.9	31.1 ± 9.9	89.6 ± 2.4	$>1 \times 10^{-5}$	nd
25	7.5 ± 2	72.3 ± 1.4	11.2 ± 1.6	31.6 ± 2.9	25 ± 11.1	68.3 ± 5.9	$>1 \times 10^{-5}$	nd
26	4.3 ± 0.89	71 ± 3.6	12 ± 2	26.6 ± 4.8	19 ± 3.75	62 ± 2.5	$>1 \times 10^{-5}$	nd
29	5.7 ± 0.17	77.3 ± 2.84	$>1 \times 10^{-5}$	nd	6.7 ± 2.8	38.3 ± 8.2	134 ± 18.7	52 ± 9
30	8.13 ± 1	63 ± 3.2	16.1 ± 6.1	26.6 ± 2.9	11.3 ± 0.6	77 ± 11	40.2 ± 29.7	23.5 ± 0.5
35	1.3 ± 0.03	30 ± 4	2.89 ± 1.25	48 ± 9.07	9.05 ± 1.5	124.5 ± 6.5	$>1 \times 10^{-5}$	nd
36	71.4 ± 14	61 ± 18	21.7 ± 9	88 ± 14	643 ± 211	78 ± 22	88 ± 23	58 ± 15
37	$>1 \times 10^{-5}$	nd	3.14 ± 0.23	97 ± 4.04	20.5 ± 7.4	97.7 ± 6.9	$>1 \times 10^{-5}$	nd
38	12.7 ± 5	34 ± 2	22 ± 12.1	52 ± 1.5	26 ± 0.8	20 ± 1	161 ± 9	60.6 ± 5.3
41	$>1 \times 10^{-5}$	nd	46.2 ± 16.2	94.75 ± 10	$>1 \times 10^{-5}$	nd	$>1 \times 10^{-5}$	nd
42	104 ± 57	50.8 ± 12.5	26.1 ± 3.6	41.4 ± 2.3	nd	nd	nd	nd
43	nd	nd	2.37 ± 1.3	79 ± 12	63 ± 12	42 ± 2	26 ± 15	22 ± 4

Concentration-response curves were analyzed by non-linear regression. Agonist potency was expressed as EC_{50} (nM) while the maximal efficacy, E_{max} 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. Data are mean of at least 3 independent experiments. nd: not determined.

14-fold, respectively), which gave a derivative with a selectivity ratio of 39. Despite suboptimal selectivity achieved with compounds **35**–**38**, it can be deduced that one of the units of the dimer does not have to be a melatonin analogue for the heterodimer to retain a good affinity and selectivity for the MT_1 receptor subtype. This conclusion confirms our assumption that the dimer does not bridge two MLT sites but that steric factors are predominantly responsible for the selectivity of our compounds. For the biphenyl series, an additional increase in affinity is due to hydrogen bond capable moiety.

Given that one pharmacophore of the bivalent ligand model could be replaced by a non-melatoninergic ligand without any loss of affinity, heterodimers with an agomelatine moiety linked to a diversely para-substituted biphenyl moiety via a four carbons chain were prepared (compounds **41**–**43**). As depicted in Table 4, compounds **42** and **43** possess subnanomolar affinities for MT_1 (0.55 and 0.09 nM, respectively) along with selectivity ratios (MT_2/MT_1 = 93 and 72, respectively) only slightly lower than that of the parent compound (**4**) (MT_2/MT_1 = 120). These results suggest that polar interactions might also play a role in the selectivity of our compounds in addition to steric factors. The hydrogen bound acceptor (**35**, **43**) appears to contribute to the affinity. Its exact effect has still to be determined.

In terms of affinity and selectivity, these two compounds seem interesting and promising as pharmacological tools. Unfortunately, like the majority of the molecules reported in this paper, they behave as partial agonists on MT_1 and MT_2 melatonin receptors subtypes. As can also be seen from Table 5, compound **41** is a full antagonist on the MT_1 receptor and five ligands (**15**, **18**, **19**, **35** and **37**) are full antagonists on MT_2 receptors. These compounds are not of major interest from a pharmacological point of view due to their partial agonist activity on the other receptor subtype. The most interesting compounds of this new series of selective melatoninergic ligands is **36**, a full antagonist on both receptor subtypes with good MT_1 and MT_2 affinities (0.37 and 4.22 nM, respectively). However, its weak selectivity (MT_2/MT_1 ratio 11) may limit its use as a pharmacological tool. Nevertheless, it is worth noting that in our binding assay on CHO cells, luzindole, a melatonin antagonist considered as selective has the same ratio of selectivity but for the MT_2 receptor.[3,31]

5. Conclusion

We successfully converted a selective MT_1 homodimer ligand into a series of asymmetric dimers with high affinity for melatonin receptors and selectivity for MT_1 ranging between 5- and 93-fold. Two compounds in this series, **42** and **43**, are among the best MT_1-selective derivatives described to date. We have also come up with an interesting compound **36** for use as a lead molecule in the development of selective MT_1 antagonist. In addition, this study showed that a bivalent ligand is not necessary to achieve MT_1 selectivity. It also confirmed the importance of a bulky substituent replacing the methoxy group of compound **1** and helped define its optimal properties. Compound **43** also hints to a possible hydrogen bonding capacity helping the affinity of a ligand.

6. Experimental section

6.1. Chemistry

Melting points were determined on a Büchi SMP-20 capillary apparatus and are uncorrected. IR spectra were recorded on a Vector 22 Bruker spectrophotometer. ^{1}H NMR spectra were recorded on an AC 300 Bruker spectrometer. Chemical shifts are reported in δ units (parts per million) relative to TMS. Mass spectra were performed on a Finnigan MAT SSQ 710 Advantage spectrometer and were recorded in the APCI positive mode. Elemental analyses for tested compounds were performed by CNRS Laboratories (Vernaison, France). Obtained results were within ±0.4% of the theoretical values.

6.1.1. *N*-[2-(7-(4-Bromobutoxy)naphthalen-1-yl)ethyl]-acetamide (14)

A mixture of **8b** (6.2 g, 27 mmol) and K_2CO_3 (18.6 g, 135 mmol) in acetonitrile (50 mL) was refluxed for 1 h. 1,4-Dibromobutane (9.7 mL, 81 mmol) was then added dropwise and the mixture was refluxed for 12 h. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in 30 mL of diethyl ether. The organic layer was washed with water, dried over $MgSO_4$ and evaporated. The residue was triturated with a mixture of isopropyl ether/petroleum ether (2:1). After filtration, the precipitate was recrystallized from isopropyl ether to give **14** (5.8 g, 15.9 mmol, 59%); mp 65–67 °C; IR (KBr) 3310 (NH), 1626 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.83 (s, 3H), 1.88–2.08 (m, 4H), 3.12 (t, J = 7.0 Hz, 2H), 3.34 (m, 2H), 3.67 (m, 2H), 4.22 (m, 2H), 7.16 (dd, J = 8.6 and 2.1 Hz, 1H), 7.22–7.34 (m, 2H), 7.61 (s, 1H), 7.70 (d, J = 7.2 Hz, 1H), 7.82 (d, J = 8.6 Hz, 1H), 8.11 (br s, 1H). Anal. ($C_{18}H_{22}BrNO$) C, H, N.

6.1.2. General procedure for the synthesis of heterodimers (15–17, 19, 22, 35, 36, 41 and 43)

The method adopted for the synthesis of *N*-[2-(7-{4-[3-(2-acetylaminoethyl)benzofuran-5-yloxy]butoxy}naphthalen-1-yl)ethyl]-acetamide (**15**) is described. A mixture of **9b** (1.0 g, 4.5 mmol) and K_2CO_3 (1.9 g, 14 mmol) in acetonitrile (70 mL) was refluxed for 30 min. **14** (1.64 g, 4.5 mmol) was then slowly added and the mixture was refluxed for 12 h. The solvent was removed under reduced pressure, and the residue was washed with a 1 M NaOH solution. The precipitate was collected by filtration, washed with water and dried. Recrystallization from acetonitrile gave **15** (1.4 g, 2.8 mmol, 62%); mp 160–162 °C; IR (KBr) 3333 (NH), 1652 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) 1.79 (s, 3H), 1.82 (s, 3H), 1.92–2.04 (m, 4H), 2.74 (t, J = 6.9 Hz, 2H), 3.11 (t, J = 8.3 Hz, 2H), 3.30–3.34 (m, 4H), 4.12 (m, 2H), 4.27 (m, 2H), 6.92 (dd, J = 8.9 and 2.2 Hz, 1H), 7.16–7.23 (m, 2H), 7.24–7.34 (m, 2H), 7.43 (d, J = 8.9 Hz, 1H), 7.62 (d, J = 1.6 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.75 (s, 1H), 7.83 (d, J = 9.3 Hz, 1H), 8.00 (br s, 1H), 8.11 (br s, 1H,). Anal. ($C_{30}H_{34}N_2O_5$) C, H, N.

6.1.3. *N*-[2-(7-{4-[3-(2-Acetylaminoethyl)benzo[*b*]thiophen-5-yloxy]butoxy}naphthalen-1-yl)ethyl] acetamide (16)

This compound was prepared from **14** (1.64 g, 4.5 mmol) and **10b** (1.06 g, 4.5 mmol) as described for **15**. Recrystallization from acetonitrile/methanol (2:1) gave **16** (1.7 g, 3.3 mmol, 73%); mp 169–170 °C; IR (KBr) 3326 (NH), 1650 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.80 (s, 3H), 1.82 (s, 3H), 1.95–2.04 (m, 4H), 2.91 (t, J = 7.1 Hz, 2H), 3.12 (t, J = 7.5 Hz, 2H), 3.35–3.39 (m, 4H), 4.18 (m, 2H), 4.28 (m, 2H), 7.04 (dd, J = 8.7 and 2.3 Hz, 1H), 7.19 (dd, J = 9.0 and 2.0 Hz, 1H), 7.23–7.32 (m, 2H), 7.41 (d, J = 2.1 Hz, 1H), 7.44 (s, 1H), 7.62 (s, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.81–7.84 (m, 2H), 8.04 (br s, 1H), 8.10 (br s, 1H). Anal. ($C_{30}H_{34}N_2O_4S$) C, H, N.

6.1.4. *N*-[2-(7-{4-[3-(2-Acetylaminoethyl)-1-benzenesulfonyl-1*H*-indol-5-yloxy]butoxy}-naphthalen-1-yl)-ethyl]acetamide (17)

This compound was prepared from **14** (1.64 g, 4.5 mmol) and **13** (1.6 g, 4.5 mmol) as described for **15**. Recrystallization from ethanol gave **17** (1.64 g, 2.56 mmol, 57%); mp 135–137 °C; IR (KBr) 3265 (NH), 1640 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.79 (s, 3H), 1.81 (s, 3H), 1.88–2.04 (m, 4H), 2.74 (m, 2H), 3.11 (m,

2H), 3.29–3.36 (m, 4H), 4.09 (m, 2H), 4.25 (m, 2H), 6.96 (d, J = 8.6 Hz, 1H), 7.16–7.30 (m, 4H), 7.78–7.95 (m, 10H), 7.98 (br s, 1H), 8.09 (br s, 1H). Anal. ($C_{36}H_{39}N_3O_6S$) C, H, N.

6.1.5. *N*-[2-(7-{4-[3-(2-Acetylaminoethyl)-1*H*-indol-5-yloxy]-butoxy}-naphthalen-1-yl)ethyl]acetamide (18)

Magnesium turnings (1.94 g, 80 mmol) and ammonium chloride (0.18 g, 3.4 mmol) were added to a solution of **17** (1.0 g, 1.5 mmol) in methanol (60 mL). The reaction mixture was stirred at room temperature for 3 h. A saturated ammonium chloride solution was added and the reaction mixture was extracted with methylene chloride. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The solid residue was recrystallized from ethanol to give **18** (0.45 g, 0.9 mmol, 60%); mp 168–170 °C; IR (KBr) 3268 (NH), 1629 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.81 (s, 3H), 1.83 (s, 3H), 1.87–2.05 (m, 4H), 2.77 (t, J = 7.2 Hz, 2H), 3.12 (t, J = 7.3 Hz, 2H), 3.27–3.36 (m, 4H), 4.08 (m, 2H), 4.27 (m, 2H), 6.75 (d, J = 9.1 Hz, 1H), 7.05 (s, 1H), 7.11 (s, 1H), 7.18–7.33 (m, 4H), 7.62 (s, 1H), 7.71 (d, J = 7.7 Hz, 1H), 7.83 (d, J = 9.1 Hz, 1H), 7.94 (br s, 1H), 8.11 (br s, 1H), 10,67 (br s, 1H). Anal. ($C_{30}H_{35}N_3O_4$) C, H, N.

6.1.6. *N*-[2-(7-{4-[8-(2-Acetylaminoethyl)-5,6,7,8-tetrahydronaphthalen-2-yloxy]butoxy} naphthalen-1-yl)ethyl]acetamide (19)

This compound was prepared from **14** (1.64 g, 4.5 mmol) and **11** (1.05 g, 4.5 mmol) as described for **15**. Recrystallization from acetonitrile gave **19** (1.53 g, 3 mmol, 66%); mp 63–65 °C; IR (KBr) 3297 (NH), 1654 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 1.56–1.82 (m, 16H), 2.61 (m, 2H), 2.71 (m, 1H), 3.08–3.13 (m, 4H), 3.32 (m, 2H), 4.03 (m, 2H), 4.24 (m, 2H), 6.65–6.74 (m, 2H), 6.93 (d, J = 8.3 Hz, 1H), 7.17 (dd, J = 8.9 Hz, J = 1.8 Hz, 1H), 7.23–7.33 (m, 2H), 7.61 (s, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.81–7.88 (m, 2H), 8.11 (br s, 1H). Anal. ($C_{32}H_{40}N_2O_4$) C, H, N.

6.1.7. [2-(7-Hydroxynaphthalen-1-yl)-ethyl]carbamic acid *tert*-butyl ester (21)

A mixture of triethylamine (3.88 mL, 280 mmol) and 2-(7-hydroxynaphthalen-1-yl)ethylamine hydrochloride **20** (3.0 g, 11 mmol) in methylene chloride (60 mL) was stirred for 30 min at 0 °C. A solution of di-*tert*-butyldicarbonate (2.3 g, 10 mmol) in methylene chloride (10 mL) was then added dropwise and the reaction mixture was stirred at room temperature for 4 h. The mixture was washed with a 0.1 M HCl solution and water. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallized from cyclohexane/toluene (1:10) to give **21** (2.87 g, 10 mmol, 91%); mp 72–73 °C; IR (KBr) 3409 (OH), 3299 (NH), 1659 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 1.37 (s, 9H), 3.03 (t, J = 7.2 Hz, 2H), 3.23 (m, 2H), 6.99 (br s, 1H), 7.09 (dd, J = 8.9 and 1.8 Hz, 1H), 7.15–7.24 (m, 2H), 7.31 (d, J = 1.8 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.9 Hz, 1H), 9.74 (br s, 1H). MS m/z: 288.3 $[M+H]^+$.

6.1.8. [2-(7-{4-[8-(2-Acetylaminoethyl)naphthalen-2-yloxy]-butoxy}naphthalen-1-yl)ethyl] carbamic acid *tert*-butyl ester (22)

This compound was prepared from **14** (1.64 g, 4.5 mmol) and **21** (1.3 g, 4.5 mmol) as described for **15**. Recrystallization from toluene gave **22** (2.06 g, 3.6 mmol, 81%); mp 101–103 °C; IR (KBr) 3330 (NH), 1691 (CO), 1639 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.37 (s, 9H), 1.81 (s, 3H), 1.99–2.04 (m, 4H), 3.10–3.13 (m, 4H), 3.20 (m, 2H), 3.32 (m, 2H), 4.28–4.32 (m, 4H), 7.09 (br s, 1H), 7.19 (dd, J = 8.9 Hz and 2.3 Hz, 2H), 7.24–7.33 (m, 4H), 7.63 (s, 2H), 7.72 (d, J = 8.1 Hz, 2H), 7.83 (d, J = 8.9 Hz, 2H), 8.11 (br s, 1H). Anal. ($C_{35}H_{42}N_2O_5$) C, H, N.

6.1.9. General procedure for the synthesis of amino derivatives (23 and 28)

The method adopted for the synthesis of *N*-[2-(7-{4-[8-(2-aminoethyl)naphthalen-2-yloxy] butoxy}naphthalen-1-yl)ethyl]acetamide hydrochloride (**23**) is described. A suspension of **22** (0.6 g, 1.1 mmol) in methanol (30 mL) was treated with gaseous HCl. After stirring for 5 h, the precipitate was collected by filtration and recrystallized from acetonitrile/methanol (3:1) to give **23** (0.44 g, 0.88 mmol, 80%); mp 188–189 °C; IR (KBr) 3332–2623 (NH_3^+), 1637 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 1.82 (s, 3H), 2.01–2.05 (m, 4H), 3.09–3.15 (m, 4H), 3.30–3.35 (m, 4H), 4.27–4.31 (m, 4H), 7.18–7.39 (m, 6H), 7.49 (s, 1H), 7.62 (s, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.83 (d, J = 9.0 Hz, 1H), 7.87 (d, J = 9.3 Hz, 1H), 8.17–8.24 (m, 4H). Anal. ($C_{30}H_{34}N_2O_3$·HCl) C, H, N.

6.1.10. General procedure for the synthesis of N-acylated derivatives (24, 25 and 29)

The method adopted for the synthesis of *N*-[2-(7-{4-[8-(2-Cyclopropanecarbonylaminoethyl) naphthalen-2-yloxy]butoxy}naphthalen-1-yl)ethyl]acetamide (**24**) is described. Potassium carbonate (0.83 g, 6 mmol) was added to a solution of **16** (1 g, 2 mmol) in water (40 mL) and chloroform (60 mL). After stirring for 20 min at 0 °C, cyclopropanecarbonyl chloride (0.23 mL, 2.2 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 30 min. The two layers were separated and the organic layer was washed with 1 M HCl solution and water, dried over $MgSO_4$ and removed in vacuo. The solid residue was recrystallized from acetonitrile to give **24** (0.8 g, 1.5 mmol, 75%); mp 154–155 °C; IR (KBr) 3321 (NH), 1625 (CO), 1636 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 0.61–0.70 (m, 4H), 1.52 (m, 1H), 1.81 (s, 3H), 2.03–2.07 (m, 4H), 3.11–3.14 (m, 4H), 3.30–3.41 (m, 4H), 4.27–4.30 (m, 4H), 7.21 (d, J = 9.0 Hz, 2H), 7.24–7.33 (m, 4H), 7.59 (d, J = 2.0 Hz, 1H), 7.62 (d, J = 2.3 Hz, 1H), 7.71 (d, J = 7.8 Hz, 2H), 7.83 (d, J = 9.0 Hz, 2H), 8.09 (br s, 1H), 8.29 (br s, 1H). Anal. ($C_{34}H_{38}N_2O_4$) C, H, N.

6.1.11. *N*-[2-(7-{4-[8-(2-(2-Furoyl)aminoethyl)naphthalen-2-yloxy]butoxy}naphthalen-1-yl}ethyl] acetamide (25)

This compound was prepared from **23** (1 g, 2 mmol) as described for **24** using 2-furoyl chloride (0.22 mL, 2.2 mmol). Recrystallization from acetonitrile gave **25** (0.9 g, 1.6 mmol, 81%); mp 148–149 °C; IR (KBr) 3337 (NH), 1649 (CO), 1624 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.81 (s, 3H), 2.01–2.06 (m, 4H), 3.11 (t, J = 7.4 Hz, 2H), 3.22 (t, J = 7.4 Hz, 2H), 3.36 (m, 2H), 3.52 (m, 2H), 4.30–4.33 (m, 4H), 6.59 (m, 1H), 7.06 (d, J = 3.6 Hz, 1H), 7.19–7.36 (m, 6H), 7.63 (s, 1H), 7.66 (s, 1H), 7.72–7.74 (m, 2H), 7.82–7.86 (m, 3H), 8.09 (br s, 1H), 8.63 (br s, 1H). Anal. ($C_{35}H_{36}N_2O_5$) C, H, N.

6.1.12. General procedure for the synthesis of *N*-acylated derivatives (26 and 30)

The method adopted for the synthesis of *N*-[2-(7-{4-[8-(2-vinylacetylaminoethyl)naphthalen-2-yloxy]butoxy} naphthalen-1-yl)-ethyl]acetamide (**26**) is described. Compound **23** (1.0 g, 2 mmol) was dissolved in water (50 mL). Sodium hydroxide (0.16 g, 4 mmol) was added and the reaction mixture was stirred for 1 h at room temperature. The mixture was then extracted with methylene chloride and dried over $MgSO_4$. Vinylacetic acid (0.29 mL, 3.4 mmol) and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (0.53 g, 3.4 mmol) were dissolved in methylene chloride (40 mL) at 0 °C. After 30 min, the solution of amine **23** was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 1 h; then, it was washed with a 1 M HCl solution and water. The organic layer was dried over $MgSO_4$, and removed under reduced pressure. The solid residue was recrystallized from acetonitrile to give **26** (0.92 g, 1.72 mmol, 86%); mp 142–143 °C; IR (KBr) 3325 (NH), 1647

(CO), 1626 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 1.81 (s, 3H), 2.01–2.05 (m, 4H), 2.88 (d, J = 7.0 Hz, 2H), 3.09–3.14 (m, 4H), 3.31–3.37 (m, 4H), 4.28–4.32 (m, 4H), 5.02–5.11 (m, 2H), 5.86 (m, 1H), 7.19 (d, J = 9.0 Hz, 2H), 7.23–7.32 (m, 4H), 7.61–7.63 (m, 2H), 7.70–7.72 (m, 2H), 7.81–7.84 (m, 2H), 8.07 (br s, 2H). Anal. ($C_{34}H_{38}N_2O_4$) C, H, N.

6.1.13. *N*-[2-(7-{4-[8-(2-*tert*-Butoxycarbonylaminoethyl)-naphthalen-2-yloxy]butoxy} naphthalen-1-yl)ethyl]carbamic acid *tert*-butyl ester (27)

A mixture of **21** (0.72 g, 2.5 mmol) and K_2CO_3 (0.83 g, 6 mmol) in acetonitrile (50 mL) was refluxed for 1 h. 1,4-Dibromobutane (0.12 mL, 1 mmol) was then added dropwise and the mixture was refluxed for 4 h. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in diethyl ether and the organic layer was washed with water, dried over $MgSO_4$ and evaporated. The residue was recrystallized from acetonitrile to give **27** (1.07 g, 1.7 mmol, 68%); mp 139–140 °C; IR (KBr) 3409 (NH), 1711 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.37 (s, 18H), 2.06 (m, 4H), 3.13 (m, 4H), 3.20 (m, 4H), 4.30 (m, 4H), 7.09 (br s, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.23–7.31 (m, 4H), 7.63 (s, 2H), 7.70 (d, J = 7.7 Hz, 2H), 7.83 (d, J = 8.7 Hz, 2H). Anal. ($C_{38}H_{48}N_2O_6$) C, H, N.

6.1.14. 2-[7-(4-{8-(2-Aminoethyl)naphthalen-2-yloxy}butoxy)-naphthalen-1-yl]ethylamine dihydrochloride (28)

This compound was prepared from **27** (0.7 g, 1.1 mmol) using gaseous HCl as described for **23**. Recrystallization from acetonitrile gave **28** (0.41 g, 0.82 mmol, 75%); mp >240 °C; IR (KBr) 2363–3140 (NH_3^+) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.03 (m, 4H), 3.06 (m, 4H), 3.38 (m, 4H), 4.32 (m, 4H), 7.23 (d, J = 8.9 Hz, 2H), 7.29 (t, J = 7.3 Hz, 2H), 7.38 (d, J = 7.0 Hz, 2H), 7.52 (s, 2H), 7.76 (d, J = 8.1 Hz, 2H), 7.86 (d, J = 8.9 Hz, 2H), 8.33 (br s, 6H). Anal. ($C_{28}H_{32}N_2O_2 \cdot 2HCl$) C, H, N.

6.1.15. *N*-[2-(7-{4-[8-(2-Cyclopropylcarbonylaminoethyl)-naphthalen-2-yloxy]butoxy} naphthalen-1-yl)ethyl]cyclopropylcarboxamide (29)

This compound was prepared from **28** (1 g, 2 mmol), using cyclopropanecarbonyl chloride (0.46 mL, 5 mmol) and potassium carbonate (1.65 g, 12 mmol) as described for **24**. Recrystallization from acetonitrile gave **29** (0.89 g, 1.58 mmol, 79%); mp 177–179 °C; IR (KBr) 3313 (NH), 1638 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 0.61–0.70 (m, 8H), 1.52 (m, 2H), 2.03 (m, 4H), 3.12 (t, J = 7.4 Hz, 4H), 3.38 (m, 4H), 4.29 (m, 4H), 7.21 (d, J = 8.7 Hz, 2H), 7.25–7.34 (m, 4H), 7.61 (s, 2H), 7.72 (d, J = 7.6 Hz, 2H), 7.83 (d, J = 8,7 Hz, 2H), 8.29 (br s, 2H). Anal. ($C_{36}H_{40}N_2O_4 \cdot 1/2H_2O$) C, H, N.

6.1.16. *N*-[2-(7-{4-[8-(2-Vinylacetylaminoethyl)naphthalen-2-yloxy]butoxy}naphthalen-1-yl)ethyl]vinylacetamide (30)

This compound was prepared from **28** (1 g, 2 mmol) using vinylacetic acid (0.58 mL, 6.8 mmol) as described for **26**. Recrystallization from acetonitrile gave **30** (0.74 g, 1.32 mmol, 66%); mp 146–148 °C; IR (KBr) 3328 (NH), 1645 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 2.05 (m, 4H), 2.88 (d, J = 6.9 Hz, 4H), 3.12 (t, J = 7.4 Hz, 4H), 3.35 (m, 4H), 4.30 (m, 4H), 5.02–5.11 (m, 4H), 5.85 (m, 2H), 7.20 (dd, J = 9.0 and 2.0 Hz, 2H), 7.22–7.31 (m, 4H), 7.61 (d, J = 2.0 Hz, 2H), 7.71 (d, J = 7.6 Hz, 2H), 7.83 (d, J = 9.0 Hz, 2H), 8.07 (br s, 2H). Anal. ($C_{36}H_{40}N_2O_4$) C, H, N.

6.1.17. General procedure for the synthesis of phenolic derivatives (31b and 32b)

The method adopted for the synthesis of (7-hydroxynaphthalen-1-yl)acetic acid (**31b**) is described. To a solution of (7-methoxynaphthalen-1-yl)acetic acid **(31a)** (5 g, 23 mmol) in acetic acid (50 mL) was added hydrobromic acid 47% (25 mL) and the mixture was refluxed for 4 h. The mixture was then removed under reduced pressure, and the residue was washed with water. After filtration, the precipitate was washed with petroleum ether and recrystallized from toluene to give **31b** (3.76 g, 18.6 mmol, 81%); mp 151–152 °C; IR (KBr) 3298 (OH), 1709 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 3.91 (s, 2H), 7.08 (dd, J = 8.8 Hz, J = 2.2 Hz, 1H), 7.12–7.24 (m, 2H), 7.33 (m, 1H), 7.71 (m, 1H), 7.79 (d, J = 8.8 Hz, 1H), 9.28 (br s, 1H), 12.39 (br s, 1H). MS *m/z*: 203.2 $[M+H]^+$.

6.1.18. 2-(6-Hydroxynaphthalen-2-yl)propionic acid (32b)

This compound was prepared from 2-(6-methoxynaphtalen-2-yl)propionic acid **(32a)** (5 g, 21 mmol) using hydrobromic acid 47% (23 mL) as described for **31b**. Recrystallization from toluene gave **32b** (3.9 g, 18.3 mmol, 87%); mp 188–189 °C; IR (KBr) 3348 (OH), 2984 (OH), 1713 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 1.43 (d, J = 7.0 Hz, 3H), 3.76 (m, 1H), 7.06–7.09 (m, 2H), 7.33 (dd, J = 8.6 Hz, J = 1.6 Hz, 1H), 7.63–7.66 (m, 2H), 7.73 (d, J = 8.6 Hz, 1H), 9.71 (br s, 1H), 12.31 (br s, 1H). MS *m/z*: 217.2 $[M+H]^+$.

6.1.19. General procedure for the synthesis of methylic esters (33 and 34)

The method adopted for the synthesis of (7-hydroxynaphthalen-1-yl)acetic acid methyl ester (**33**) is described. Thionyl chloride (3.24 mL, 44.4 mmol) was slowly added to a solution of **31** (3 g, 14.8 mmol) in methanol (50 mL) at 0 °C. The mixture was kept at 0 °C for 20 min and stirred at room temperature for 1 h. The methanol was removed under reduced pressure and the residue was recrystallized from cyclohexane/toluene (1:4) to give **33** (2.78 g, 12.9 mmol, 87%); mp 115–116 °C; IR (KBr) 3298 (OH), 1716 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 3.63 (s, 3H), 4.01 (s, 2H), 7.11 (dd, J = 9.0 Hz, J = 2.2 Hz, 1H), 7.15 (d, J = 2.2 Hz, 1H), 7.22 (m, 1H), 7.35 (m, 1H), 7.73 (m, 1H), 7.78 (d, J = 9.0 Hz, 1H), 9.08 (br s, 1H). MS *m/z*: 217.23 $[M+H]^+$.

6.1.20. 2-(6-Hydroxynaphthalen-2-yl)propionic acid methyl ester (34)

This compound was prepared from **32** (3 g, 14 mmol) using thionyl chloride (3.04 ml, 41.7 mmol) as described for **33**. Recrystallization from cyclohexane gave **34** (2.35 g, 10.2 mmol, 73%); mp 81–82 °C; IR (KBr) 3367 (OH), 1708 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 1.45 (d, J = 7.0 Hz, 3H), 3.59 (s, 3H), 3.88 (m, 1H), 7.06–7.09 (m, 2H), 7.3 (dd, J = 8.6 Hz, J = 1.6 Hz, 1H), 7.64–7.65 (m, 2H), 7.73 (d, J = 8.6 Hz, 1H), 9.71 (br s, 1H). MS *m/z*: 231.3 $[M+H]^+$.

6.1.21. *N*-[2-(7-{4-[8-(Methoxycarbonylmethyl)naphthalen-2-yloxy]butoxy}naphthalen-1-yl)ethyl] acetamide (35)

This compound was prepared from **14** (1.67 g, 4.6 mmol) and **33** (1 g, 4.6 mmol) as described for **15**. Recrystallization from methanol gave **35** (1.77 g, 3.54 mmol, 77%); mp 109–110 °C; IR (KBr) 3331 (NH), 1727 (CO), 1632 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 1.82 (s, 3H), 2.01–2.04 (m, 4H), 3.12 (t, J = 7.3 Hz, 2H), 3.33 (m, 2H), 3.60 (s, 3H), 4.11 (s, 2H), 4.22 (m, 2H), 4.29 (m, 2H), 7.02–7.33 (m, 6H), 7.39 (d, J = 6.1 Hz, 1H), 7.63 (d, J = 1.9 Hz, 1H), 7.71 (d, J = 7.1 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.82–7.88 (m, 2H), 8.10 (br s, 1H). Anal. ($C_{31}H_{33}NO_5$) C, H, N.

6.1.22. *N*-[2-(7-{4-[6-(1-Methoxycarbonylethyl)naphthalen-2-yloxy]butoxy}naphthalen-1-yl)ethyl] acetamide (36)

This compound was prepared from **14** (1.64 g, 4.5 mmol) and **34** (1.03 g, 4.5 mmol) as described for **15**. Recrystallization from toluene give **36** (1.15 g, 2.25 mmol, 50%); mp 116–117 °C; IR (KBr) 3276 (NH), 1735 (CO), 1637 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 1.50 (d, J = 7.3 Hz, 3H), 1.82 (s, 3H), 2.01–2.04 (m, 4H), 3.12 (m, 2H), 3.37 (m, 2H), 3.62 (s, 3H), 4.11 (q, J = 7.3 Hz, 1H),

4.22 (m, 2H), 4.29 (m, 2H), 7.15–7.20 (m, 2H), 7.22–7.33 (m, 3H), 7.38 (dd, J = 8.5 Hz, J = 1.7 Hz, 1H), 7.60 (d, J = 2.2 Hz, 1H), 7.68–7.76 (m, 4H), 7.80–7.85 (m, 2H). Anal. ($C_{32}H_{35}NO_5$) C, H, N.

6.1.23. General procedure for the synthesis of carboxy derivatives (37, 38, and 42)

The method adopted for the synthesis of *N*-[2-{7-(4-[8-(carboxymethyl)naphthalen-2-yloxy] butoxy) naphthalen-1-yl}ethyl]acetamide (**37**) is described. To a solution of **35** (1 g, 2 mmol) in THF (25 mL) and methanol (15 mL) was added a solution of sodium hydroxide (0.24 g, 6 mmol) in water (15 mL). The mixture was stirred at room temperature for 4 h. After concentration under reduced pressure, the mixture was acidified with 1 M HCl. The precipitate was then collected by filtration and recrystallized from methanol to give **37** (0.65 g, 1.34 mmol, 67%); mp 131–132 °C; IR (KBr) 3329 (NH), 2933 (OH), 1697 (CO), 1629 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 1.83 (s, 3H), 2.01–2.04 (m, 4H), 3.12 (t, J = 7.3 Hz, 2H), 3.34 (m, 2H), 4.00 (s, 2H), 4.21 (m, 2H), 4.29 (m, 2H), 7.19–7.34 (m, 6H), 7.39 (d, J = 7.0 Hz, 1H), 7.63 (s, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.82–7.88 (m, 2H), 8.10 (br s, 1H), 12.44 (br s, 1H). Anal. ($C_{30}H_{31}NO_5$) C, H, N.

6.1.24. *N*-[2-(7-{4-[6-(1-Carboxyethyl)naphthalen-2-yloxy]-butoxy}naphthalen-1-yl)ethyl]acetamide (38)

This compound was prepared from **36** (1 g, 1.9 mmol) using sodium hydroxide (0.023 g, 5.7 mmol) as described for **37**. Recrystallization from toluene gave **38** (0.39 g, 0.78 mmol, 41%); mp 142–143 °C; IR (KBr) 3274 (NH) 2874 (OH), 1704 (CO), 1627 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 1.44 (d, J = 7.3 Hz, 3H), 1.82 (s, 3H), 2.00–2.05 (m, 4H), 3.11 (t, J = 8.5 Hz, 2H), 3.35 (m, 2H), 3.78 (q, J = 7.3 Hz, 1H), 4.20 (m, 2H), 4.28 (m, 2H), 7.14–7.21 (m, 2H), 7.23–7.34 (m, 3H), 7.38 (d, J = 8.5 Hz, 1H), 7.62 (s, 1H), 7.68–7.76 (m, 3H), 7.80–7.85 (m, 2H), 8.12 (br s, 1H), 12.33 (br s, 1H). Anal. ($C_{31}H_{33}NO_5$) C, H, N.

6.1.25. 4′-Hydroxy[1,1′-biphenyl]-4-carboxylic acid methyl ester (39)

This compound was prepared from 4-(4′-hydroxyphenyl)benzoic acid (3 g, 14 mmol) using thionyl chloride (3.1 mL, 42 mmol) as described for **33**. Recrystallization from acetonitrile gave **39** (2.4 g, 10.5 mmol, 75%); mp 231–233 °C; IR (KBr) 3401 (OH), 1689 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 3.86 (s, 3H), 6.88 (dd, J = 6.8 Hz, J = 1.9 Hz, 2H), 7.58 (dd, J = 6.8 Hz, J = 1.9 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H), 9.76 (br s, 1H). MS m/z: 229.2 $[M+H]^+$.

6.1.26. 4′-Hydroxy[1,1′-biphenyl]-4-methanol (40)

To a suspension of $LiAlH_4$ (1.14 g, 30 mmol) in THF (80 mL) at 0 °C was added dropwise a solution of **39** (3.3 g, 15 mmol) in dry THF (30 mL). The reaction mixture was stirred 30 min. at 0 °C and 48 h at room temperature. The mixture was then cooled down with an ice bath and water (1.1 mL) was added, followed by a 15% NaOH aqueous solution (1.1 mL) and water (2.2 mL). The mixture was filtered and the solid was washed with ether. The filtrate was evaporated and the crude product was recrystallized from toluene to give **40** (2.28 g, 11.4 mmol, 76%); mp 198–199 °C; IR (KBr) 3387 (OH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 4.51 (d, J = 5.3 Hz, 2H), 5.19 (m, 1H), 6.85 (dd, J = 6.8 Hz, J = 1.9 Hz, 2H), 7.34 (dd, J = 6.8 Hz, J = 1.9 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H), 9.53 (br s, 1H). MS m/z: 201.3 $[M+H]^+$.

6.1.27. *N*-[2-(7-{4-[4′-Methoxycarbonylbiphenyl-4-yloxy]-butoxy}naphthalen-1-yl)ethyl] acetamide (41)

This compound was prepared from **14** (1.64 g, 4.5 mmol) and **39** (1.02 g, 4.5 mmol) as described for **15**. Recrystallization from acetonitrile give **41** (1.63 g, 3.2 mmol, 71%); mp 166–168 °C; IR (KBr) 3313 (OH), 1728 (CO), 1638 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 1.82 (s, 3H), 1.95–2.03 (m, 4H), 3.11 (t, J = 7.2 Hz, 2H), 3.32 (m, 2H), 3.87 (s, 3H), 4.15 (m, 2H), 4.27 (m, 2H), 7.08 (d, J = 8.6 Hz, 2H), 7.18 (dd, J = 8.9 Hz, J = 2.1 Hz, 1H), 7.24–7.32 (m, 2H), 7.63 (s, 1H), 7.68–7.73 (m, 3H), 7.77–7.84 (m, 3H), 8.01 (d, J = 8.2 Hz, 2H), 8.11 (br s, 1H). Anal. ($C_{32}H_{33}NO_5$) C, H, N.

6.1.28. *N*-[2-(7-{4-(4′-Carboxybiphenyl-4-yloxy)butoxy}-naphthalen-1-yl)ethyl]acetamide (42)

This compound was prepared from **41** (1 g, 1.9 mmol) using sodium hydroxide (0.23 g, 5.7 mmol) as described for **37**. Recrystallization from DMF gave **42** (0.56 g, 1.14 mmol, 60%); mp 223–225 °C; IR (KBr) 3301 (NH), 2952 (OH), 1674 (CO), 1625 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 1.82 (s, 3H), 1.95–2.03 (m, 4H), 3.11 (t, J = 7.2 Hz, 2H), 3.31 (m, 2H), 4.16 (m, 2H), 4.28 (m, 2H), 7.09 (d, J = 8.7 Hz, 2H), 7.17 (dd, J = 9.2 Hz, J = 2.3 Hz, 1H), 7.20–7.33 (m, 2H), 7.62 (s, 1H), 7.68–7.73 (m, 5H), 7.84 (d, J = 9.2 Hz, 1H), 7.99 (d, J = 8.2 Hz, 2H), 8.13 (br s, 1H), 11.98 (br s, 1H). Anal. ($C_{31}H_{31}NO_5$) C, H, N.

6.1.29. *N*-[2-(7-{4-(4′-Hydroxymethylbiphenyl-4-yloxy}butoxy)-naphthalen-1-yl)ethyl]acetamide (43)

This compound was prepared from **14** (1.82 g, 5 mmol) and **40** (1 g, 5 mmol) as described for **15**. Recrystallization from acetonitrile give **43** (1.33 g, 2.75 mmol, 55%); mp 172–173 °C; IR (KBr) 3331 (NH, OH), 1643 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 1.83 (s, 3H), 1.97–2.05 (m, 4H), 3.11 (t, J = 7.2 Hz, 2H), 3.33 (m, 2H), 4.13 (m, 2H), 4.27 (m, 2H), 4.52 (d, J = 5.5 Hz, 2H), 5.20 (t, J = 5.5 Hz, 1H), 7.09 (d, J = 8.7 Hz, 2H), 7.17 (dd, J = 9.0 Hz, J = 2.3 Hz, 1H), 7.19–7.30 (m, 4H), 7.55–7.59 (m, 4H), 7.62 (d, J = 2.3 Hz, 1H), 7.84 (d, J = 7.4 Hz, 1H), 7.99 (d, J = 8.9 Hz, 1H), 8.12 (br s, 1H). Anal. ($C_{31}H_{33}NO_4$) C, H, N.

6.2. Pharmacological methods

6.2.1. 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).

6.2.2. Cell culture

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 (95,000*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.

6.2.3. Binding assays

2-[^{125}I]-iodomelatonin binding assay conditions were essentially as previously described.[31] Briefly, binding was initiated by addition of membrane preparations from stable transfected CHO cells diluted in binding buffer (50 mM Tris/HCl buffer, pH 7.4 containing 5 mM $MgCl_2$) to 2-[^{125}I]-iodomelatonin (20 pM for MT_1 and MT_2 receptors) and the tested drug. Nonspecific 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/HCl buffer, pH 7.4.

Data from the dose–response curves (seven concentrations in duplicate) were analysed 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 characterising the membrane preparation.

[^{35}S]-GTPγS binding assay was performed according to published methodology.[31] Briefly, membranes from transfected CHO cells expressing MT_1 or 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 pre-incubated with both the melatonin (30 or 3 nM for hMT_1 and hMT_2 receptors, respectively) 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 GTPγS 10 μM which defined the non specific binding. Data from the dose–response curves (seven concentrations in duplicate) were analysed 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 30 or 3 nM for hMT_1 and hMT_2 receptors, respectively.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2010.04.008.

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