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Research paper

Synthesis of 2-arylfuro[3,2-*b*]pyridines: Effect of the *C*2-aryl group on melatoninergic activity

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ABSTRACT

We report herein an efficient synthesis of 2-substituted furo[3,2-*b*]pyridines and their biological evaluation as melatonin receptors ligands. The proposed eight-step sequence ending with a Suzuki coupling allowed a rapid access to various analogues. The steric hindrance and the conformation of the aryl group in *C*2-position were evaluated regarding the selectivity of the molecule for one of the two high affinity melatonin receptors as well as the activity profile of the compound. Introduction of 1-naphthyl substituent gave the best result in terms of selectivity with a MT_1/MT_2 ratio of about 150 (MT_1 K_i = 198 nM, MT_2 K_i = 1.3 nM).

1. Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine, **I**, Fig. 1) is a neurohormone which is synthesized and secreted in the pineal gland during the period of darkness. This hormone acts as a regulator of the biological clock and is involved in several physiological and metabolic processes including central nervous system disorders [1–4]. Moreover, melatonin has been described as anti-inflammatory [5], pain modulator [6], antioxidant [7,8], retinal [9], vascular [10] and antitumoral agent [11]. However, melatonin is not often used in clinical treatments due to its short half-life [12] but it is used as a dietary complement. Research on melatonin analogues lead to the marketing of Ramelteon (Rozerem®), a melatonin agonist, employed to treat insomnia and nocturia [13]. Since 2009, a melatonin receptor agonist and a 5-HT_{2C} antagonist, Agomelatine (Valdoxan®), is indicated for the treatment of depression [14].

Biological functions of melatonin are mediated through activation of two high affinity G-protein coupled receptors MT_1 and MT_2 [15–17]. The mechanism of action of melatonin is getting an increasing interest and one of the challenges is to develop MT_1-or MT_2-selective ligands as pharmacological tools to understand the function of each receptor subtypes. Recently, many series of MT_2-selective ligands have been reported, such as ligand **II** [18] (Fig. 1), with selectivity ratios from good (124-fold) to excellent (until 1200-fold) [19–23]. However, full agonist selective ligands are still required to explain the intrinsic biological properties of MT_2. Subtype selectivity seems to be correlated with the presence in the *C*2-position of a hydrophobic aryl substituent out-of-the-plane of the *core* skeleton [24,25]. *C*2-arylation might also be responsible for the antagonist behavior observed for a lot of MT_2 selective ligands [18,26].

Among all melatonin analogues (biological affinity are reported in Table 1), the benzofuran scaffold (Fig. 1, ligand **III**) appeared to be as efficient as the original indole skeleton [27]. The furo[2,3-*c*] pyridine ligand (Fig. 1, ligand **Vb**) has been previously synthesized in our group [28] and biologically evaluated on MT receptors. It showed a good activity on both MT_1 and MT_2 receptors [29], however, it was not the most potent melatoninergic ligand we could expect. Indeed, in the pyrrolopyridine series, the 4-azaindole isomer (Fig. 1, ligand **IVa**) gives a best biological profile than the 6- and 7-azaindoles (Fig. 1, ligands **IVb** and **IVc** respectively) [30], and confirmed by the MT_2-selective radioligand recently published [31]. As a result, we chose to work on the furo[3,2-*b*]pyridine series

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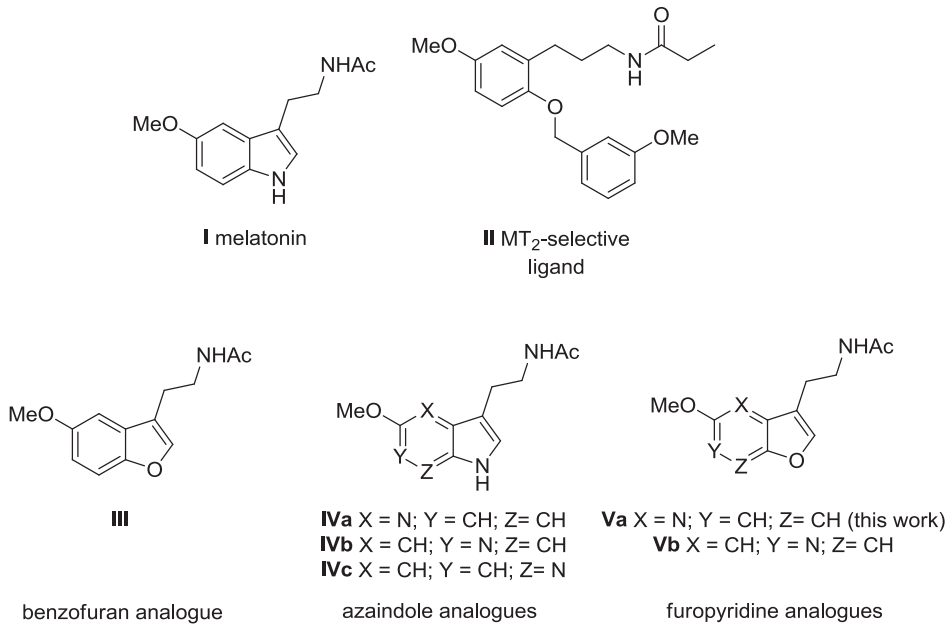


Fig. 1. Natural neurohormone **I**, MT_2-selective ligand **II**, benzofuran analogue **III**, azaindole and furopyridine derivatives **IVa**–**c** and **Va**–**b**.

Table 1
Biological bindings.

Compound	$K_i \pm$ SEM (nM)		Selectivity fold MT_1/MT_2
	MT_1	MT_2	
I	0.25 ± 0.09	0.34 ± 0.09	0.7
II	1350	1.7	790
III	0.15 ± 0.02	0.34 ± 0.02	0.5
IVa	0.24 ± 0.004	0.36 ± 0.6	0.7
IVb	9.5 ± 2.2	35 ± 2.6	0.3
IVc	40 ± 5.1	117 ± 12	0.3
Vb	73 ± 11	59 ± 15	1.2

(Fig. 1, ligand **Va**) as an hybrid pattern between benzofuran and 4-azaindole scaffolds. The methodology we previously developed using a palladium-copper catalyzed synthesis of the furopyridine ring described was not convenient for an easy modulation of substituents at position *C*2. For each new substituent, the reaction conditions had to be adjusted. To avoid the weakness of this previous strategy, we herein presented the development of a new synthetic pathway to access structures derived from furo[3,2-*b*] pyridines (Fig. 1, **Va**). Our new methodology ends with a Suzuki-Miyaura cross-coupling at *C*2 position, allowing a wide range of substituents to be coupled.

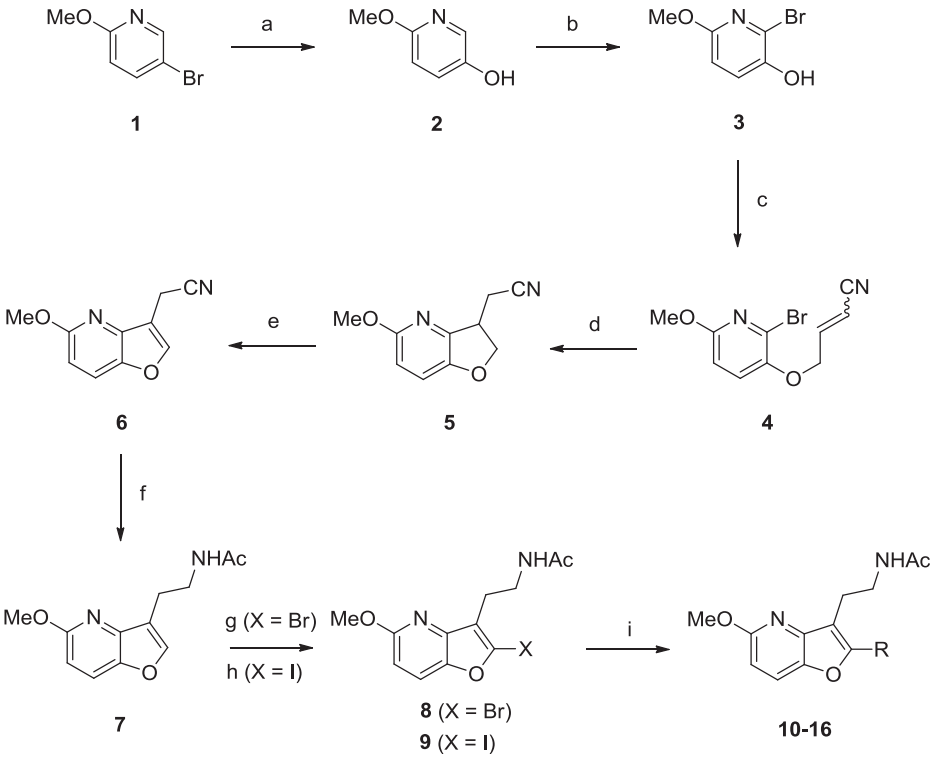
2. Chemistry

*C*2-substituted furopyridines were prepared as shown in Scheme 1. First, the 5-methoxy-3-pyridinol **2** was successfully synthesized from commercially available 5-bromo-2-methoxypyridine **1** in a one-pot three-steps sequence in a good 57% overall yield: 5-bromo-2-methoxypyridine **1** initially underwent an halogen-metal exchange at low temperature followed by the lithiated species trapping with trimethylborate and subsequent oxidation step of the aryldimethylborate with peracetic acid at 0 °C [32]. Regioselective bromination of **2** was carried out with *N*-bromosuccinimide in acetonitrile to afford **3** in good 73% yield. In order to build the furanic cycle and to introduce the 2-ethylacetamide side chain precursor in one step, pyridinol **3** was deprotonated with sodium hydride in acetonitrile and was subjected to an *O*-alkylation with 4-bromobut-2-enenitrile [33] to yield a 65/35 *Z*/*E* mixture of 4-((2-bromo-6-methoxypyridin-3-yl)oxy)but-2-enenitrile **4** in 88% yield. Radical cyclization of the *Z*/*E* mixture of **4** and formation of the dihydrofurane ring was achieved with tributyltin hydride (3 equivalents) in the presence of AIBN (30 mol %) to yield dihydrofuropyridine **5** as a single regioisomer: the 5-*exo-trig* adduct was isolated in 78% yield. The oxidation of compound **5** was carried out with *o*-chloranil to afford the furopyridine skeleton **6** in 55% yield [34]. Despite our efforts to optimize this aromatization step, full oxidation of dihydrofuropyridine **5** into furopyridine **6** was unachievable and 30% of starting material (which were engaged in a new aromatization process) were recovered. Direct conversion of the nitrile-bearing furopyridine **6** into 2-ethylacetamide **7** was achieved in a one-pot reaction: Raney nickel-catalyzed hydrogenation (5 bar) in acetic anhydride with sodium acetate gave 2-ethylacetamide **7** in 50% overall yield. Access to the targeted products by Suzuki-Miyaura cross-coupling reaction first required the halogenation of the 3-substituted furopyridine **7** at position *C*2. Bromination reaction was performed at low temperature by metalation and electrophilic trapping with carbon tetrabromide to afford **8** [35], while iodination was achieved using iodine as electrophile to afford the iodo derivative **9**. The last step of the synthesis consists in a Suzuki-Miyaura cross coupling reaction between compound **8** and different boronic acids to afford the 2-substituted furopyridines **10**–**16**. This step can also be performed from **9** as shown with the phenyl boronic acid and afford the 2-phenylfuro[3,2-*b*] analogue **10** in 80% yield. Yields and final structures are described in Table 2.

The main advantage of this new synthetic pathway to 2-substituted furo[3,2-*b*]pyridines is the large range of substituent that could be introduced in the last step in very good yields after a straightforward sequence.

3. Biological assays

The binding affinities of the final compounds **10**–**16** and also of compounds **7** and **9** were determined in competition radioligand binding assays using 2-[^{125}I]-iodomelatonin on human MT_1 and



Scheme 1. Synthetic pathway to 2-substituted furo[3,2-*b*]pyridines. *Reagents and conditions*: a) i) *n*-BuLi (1.5 eq.), THF, −78 °C, 20 min; ii) $B(OMe)_3$ (1.5 eq.), −78 °C, 2 h; iii) CH_3CO_3H (1.5 eq.), 0 °C, 1 h; iv) $NaHCO_3$ (1.5 eq.), r.t., 1 h, 57%; b) NBS (1.1 eq.), MeCN, r.t., 2 h, 73%; c) NaH (1.5 eq.), MeCN, 0 °C, 30 min then 4-bromobut-2-enenitrile (2 eq.), r.t., overnight, 88%; d) Bu_3SnH (3 eq.), AIBN (0.3 eq.), benzene, reflux, 24 h-48 h, 78%; e) *o*-chloranil (2 eq.), toluene, reflux, 24 h, 55%; f) Ac_2O, NaOAc (1.5 eq.), Raney Ni (cat.), H_2 (5 bar), 60 °C, 24 h, 60%; g) *n*-BuLi (10 eq.), THF, −78 °C, 1 h then CBr_4 (2 eq.) in THF, −78 °C, 1 h, 67%; h) *n*-BuLi (10 eq.), THF, −78 °C, 1 h then I_2 (2 eq.) in THF, −78 °C, 1 h, 52%; i) Cs_2CO_3 (6 eq.), boronic acid (1.5 eq.), $Pd(PPh_3)_4$ (5 mol%), water/dioxane (1/2).

MT_2 receptors expressed in HEK-293 cells.

The activity behaviors are evaluated by the [^{35}S]-GTPγS binding assay performed on membranes from CHO cells.

Results in binding affinities as well as activity behaviors and MT_1/MT_2 selectivity ratios are reported in Table 3.

4. Results and discussion

Compared to 4-azaindole **IVa**, compound **7** shows slightly lower affinities for MT_1 and MT_2 receptors but remains a very good melatoninergic ligand. The introduction of the bulky iodine atom improves the affinity for MT_1 and MT_2 by 8 and 15 times respectively. This tendency is in agreement with the improve affinity of 2-iodomelatonin vs melatonin [36]. The introduction of a phenyl group or a 4-fluorophenyl group at the *C*2-position leads to **10** and **11**, presenting similar binding profiles compared to the iodinated derivative with subnanomolar affinities. These four ligands exhibit no selectivity toward MT_2 and behave as full agonists for both melatonin receptors.

Replacement of the phenyl group by the 2,6-dimethylphenyl group causes a loss of affinity for melatoninergic binding sites. This might be due to the orthogonal positioning of the aryl group towards the plan *core*. Compared to **10**, the activity of the resulting ligand **12** is also modified from an agonist profile on MT_1 and MT_2 to an antagonist profile towards MT_1 subtype and partial agonist profile on MT_2 subtype.

Introduction of 1-naphthyl in *C*2-position maintains a good affinity for the MT_2 receptor but leads to a sharp decrease in MT_1 affinity (124-fold compared to **7**, 4900-fold compared to **10**). This loss of affinity for MT_1 subtype results in an enhancement of the selectivity ratio, up to 152, and gives the best ligand in the series. Compound **14** with a 2-naphthyl group in *C*2, exhibits a sharp loss of selectivity due to good affinities for each receptor subtype. Both ligands are MT_2 antagonists but **13** behaves as an MT_1 antagonist while **14** behaves as an MT_1 agonist. Once again, as for **12**, the MT_1 antagonism of **13** might be explained by the perpendicular orientation of the 1-naphthyl group from the indole.

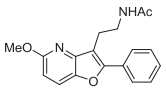
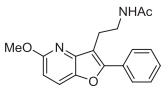
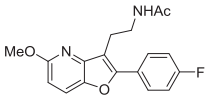
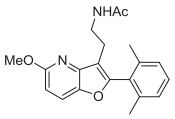
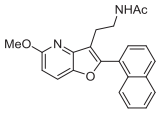
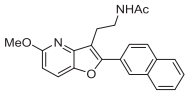
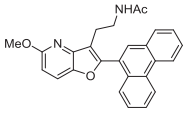
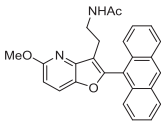
Increasing once more the size of the substituent leads to compounds **15** and **16**, bearing at the *C*2 position a 9-anthracenyl and a 9-phenanthrenyl group respectively. The increase steric hindrance resulted in low binding affinities and even decreased selectivity ratios but confirmed the MT_2 antagonist profile of C-2 steric hindered ligands [37]. Although the *C*2-aryl groups might be positioned in an orthogonal way from the plane *core* nucleus, **15** and **16** show partial agonist profiles at MT_1, which can be attributed to the bigger steric factors.

5. Conclusion

We described herein a new synthetic pathway towards *C*2-substituted furo[3,2-*b*]pyridines in an eight-steps sequence. A large range of aryl substituents can be easily and efficiently introduced thanks to this methodology.

In the furo[3,2-b]pyridine series we have developed three compounds (**9**, **10**, **11**) with subnanomolar binding affinities and MT_1/MT_2 agonist activities. Ligand **13** exhibits a 152-fold selectivity ratio for MT_2 receptors and behaves as an antagonist towards both melatoninergic receptors. Other analogues bearing bulky groups a perpendicular conformation show only moderate selectivity ratios for MT_2 receptor but seem to behave as MT_1 antagonists

Table 2
Structures and yields for compounds **10**–**16** from the Suzuki-Miyaura cross-coupling reaction.

Entry	Starting material	Compound	Structure	Yield (%)[a]
1	**8**	**10**		90
2	**9**	**10**		80
3	**8**	**11**		78
4	**8**	**12**		87
5	**8**	**13**		83
6	**8**	**14**		60
7	**8**	**15**		80
8	**8**	**16**		95

[a] Isolated yield after column chromatography.

6. Experimental section

6.1. Chemistry

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 250 MHz or 400 MHz instrument using $CDCl_3$. The chemical shifts are reported in part per million (δ scale in ppm) and all coupling constant (J) values are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet doublet) and bs (broad singlet). Melting points are uncorrected. IR absorption spectra were obtained on a Perkin Elmer PARAGON 1000 PC and values are reported in cm^{-1}. HRMS were recorded on a Maxis Bruker instrument. Column chromatographies were performed using silica gel 60 (0.063–0.200 mm, Merck).

6.1.1. 6-Methoxypyridin-3-ol (**2**)

Under argon, *n*-butyllitium (20 mL, 31.8 mmol) was added dropwise to a solution of **1** (4 g, 21.3 mmol) in THF (140 mL) cooled to − 78 °C. After 20 min, trimethylborate (3.7 mL, 31.8 mmol) was added slowly and the media is stirred at −78 °C for 2 h. A solution of peracetic acid (6.7 mL, 31.8 mmol) was added and the media was allowed to warm to 0 °C. After 1 h at 0 °C, the reaction was quenched with an aqueous solution of $NaHCO_3$ and allowed to warm to r.t. The media is partially concentrated, diluted in DCM and washed with water. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (SiO_2, 7/3 petroleum ether/EtOAc) to afford **2** as a yellow solid. Yield: 57%; m.p.: 77–79 °C; IR (ATR Diamond, cm^{-1}) ν 3050, 2660, 1601, 1497, 1262, 1047; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.9 (s, 3H, OCH_3), 6.7 (d, 1H, J = 8.9 Hz, H_5), 7.2 (dd, 1H, J = 8.9 Hz, J = 3.0 Hz, H_4), 7.8 (d, 1H, J = 3.0 Hz, H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54 (CH_3), 111 (CH), 129 (CH), 133 (CH), 148 (Cq), 159 (Cq); HRMS (EI-MS): calculated for $C_6H_8NO_2$ 126.05495 $[M+H]^+$ found 126.05530 $[M+H]^+$.

6.1.2. 2-Bromo-6-methoxypyridin-3-ol (**3**)

N-bromosuccinimide (1.4 g, 7.9 mmol) was added to a solution of **2** (900 mg, 7.2 mmol) in acetonitrile (30 mL) and the mixture was stirred during 2 h at r.t. The media was quenched with water and extracted 3 times with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (SiO_2, 9/1 petroleum ether/EtOAc) to afford **3** as a yellow solid. Yield: 73%; m.p.: 86–88 °C; IR (ATR Diamond, cm^{-1}) ν 2941, 2845, 1571, 1547, 1476, 1274, 1041, 810; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.9 (s, 3H, OCH_3), 5.0 (bs, 1H, OH), 6.7 (d, 1H, J = 8.6 Hz, H_5), 7.3 (d, 1H, J = 8.6 Hz, H_4); ^{13}C (100 MHz, $CDCl_3$) δ 54 (CH_3), 111 (CH), 125 (Cq), 127 (CH), 144 (Cq), 157 (Cq); HRMS (EI-MS): calculated for $C_6H_7BrNO_2$ 203.96546 $[M+H]^+$ found 203.96574 $[M+H]^+$.

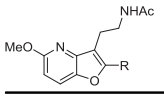
6.1.3. 4-((2-Bromo-6-methoxypyridin-3-yl)oxy)but-2-enenitrile (**4**)

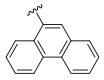
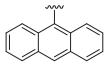
Under argon, sodium hydride (150 mg, 3.7 mmol) was added portionwise to a solution of **3** (500 mg, 2.5 mmol) in freshly distilled acetonitrile (15 mL) cooled to 0 °C. The mixture was stirred at 0 °C for 30 min and 4-bromobut-2-enenitrile (540 mg, 3.7 mmol) was added. The solution was allowed to warm to r.t. and was stirred at r.t. overnight. The media was quenched with water and extracted 3 times with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (SiO_2, 9/1 petroleum ether/EtOAc) to afford compound **4** as a brown oil (*cis* isomer) and a white solid (*trans* isomer). Global yield: 88% (*cis*/*trans* ratio = 65/35); m.p. *trans* isomer: 100–102 °C; IR (ATR Diamond, cm^{-1}) ν 3056, 2220, 1471, 1254, 1096,1054, 816; ^{1}H NMR (400 MHz, $CDCl_3$) δ *cis* isomer 3.9 (s, 3H, OCH_3), 4.9 (dd, 2H, J = 6.1 Hz, J = 1.7 Hz, H_8), 5.6 (dt, 1H, J = 11.2 Hz, J = 1.7 Hz, H_{10}), 6.7 (d, 1H, J = 8.7 Hz, H_5), 6.8 (dt, 1H, J = 11.2 Hz, J = 6.1 Hz, H_9), 7.3 (d, 1H, J = 8.7 Hz, H_4) *trans* isomer 3.9 (s, 3H, OCH_3), 4.7 (dd, 2H, J = 3.5 Hz, J = 2.4 Hz, H_8), 6.0 (dt, 1H, J = 16.3 Hz, J = 2.4 Hz, H_{10}), 6.7 (d, 1H, J = 8.8 Hz, H_5), 6.8 (dt, 1H, J = 16.3 Hz, J = 3.5 Hz, H_9), 7.2 (d, 1H, J = 8.8 Hz, H_4); ^{13}C NMR (100 MHz, $CDCl_3$) δ *cis* isomer 54 (CH_3), 69 (CH_2), 102 (CH), 110 (CH), 115 (CN), 128 (CH), 130 (Cq), 146 (Cq), 148 (CH), 159 (Cq) *trans* isomer 55 (CH_3), 69 (CH_2), 102 (CH), 110 (CH), 117 (CN), 127 (CH), 130 (Cq), 146 (Cq), 148 (CH), 159 (Cq); HRMS (EI-MS): calculated for $C_{10}H_{10}BrNO_2$ 268.99202 $[M+H]^+$ found *cis* isomer 268.99186 $[M+H]^+$ and found *trans* isomer 268.99193 $[M+H]^+$.

6.1.4. 2-(5-Methoxy-2,3-dihydrofuro[3,2-b]pyridin-3-yl) acetonitrile (**5**)

Under argon, tributyltin hydride (2 mL, 11.1 mmol) and AIBN (180 mg, 1.1 mmol) were added to a solution of **4** (1 g, 3.7 mmol) in degassed benzene (100 mL). The mixture was stirred under reflux for 24–48 h. The media was partially concentrated and acetone (50 mL) and a saturated aqueous solution of potassium fluoride (50 mL) were added. After precipitation of tin salts, the media was filtered through a silica pad. The filtrate was partially concentrated and the resulting aqueous phase was extracted 3 times with EtOAc. The combined organic layers were washed with NH_4Cl, dried over $MgSO_4$ and concentrated. The residue was dissolved in acetonitrile

Table 3
Biological assay results.



Compound	R	$K_i \pm$ SEM (nM)		Selectivity fold MT_1/MT_2	Activity
		MT_1	MT_2		
7	H	1.6 ± 0.2	1.2 ± 0.3	1.5	Agonist MT_1 Agonist MT_2
9	I	0.2 ± 0.5	0.08 ± 0.01	2.5	Agonist MT_1 Agonist MT_2
10		0.04 ± 0.003	0.14 ± 0.04	0.3	Agonist MT_1 Agonist MT_2
11		0.2 ± 0.04	0.03 ± 0.009	6.7	Agonist MT_1 Agonist MT_2
12		120 ± 14	9 ± 0.7	13.3	Antagonist MT_1 Partial agonist MT_2
13		198 ± 18	1.3 ± 0.2	152.3	Antagonist MT_1 Antagonist MT_2
14		2.2 ± 0.2	0.09 ± 0.003	22.2	Agonist MT_1 Antagonist MT_2
15		31 ± 0.5	5 ± 0.4	6.2	Partial agonist MT_1 Antagonist MT_2
16		68 ± 7	5 ± 0.3	13.6	Partial agonist MT_1 Antagonist MT_2

and washed with hexane to afford compound **5** as a yellow oil. Yield: 78%; IR (ATR Diamond, cm^{-1}) ν 2953, 2248, 1472, 1418, 1232, 1024; ^1H NMR (250 MHz, $CDCl_3$) δ 2.7 (dd, 1H, $J = 17.0$ Hz, $J = 8.5$ Hz, H_{10a}), 2.9 (dd, 1H, $J = 17.0$ Hz, $J = 4.5$ Hz, H_{10b}), 3.7–3.8 (m, 1H, H_9), 3.9 (s, 3H, OCH_3), 4.4 (dd, 1H, $J = 10.0$ Hz, $J = 6.5$ Hz, H_{8a}), 4.8–4.9 (m, 1H, H_{8b}), 6.6 (d, 1H, $J = 8.8$ Hz, H_5), 7.1 (d, 1H, $J = 8.8$ Hz, H_4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21 (CH_2), 40 (CH), 54 (CH_3), 75 (CH_2), 110 (CH), 118 (CN), 121 (CH), 144 (Cq), 148 (Cq), 160 (Cq); HRMS (EI-MS): calculated for $C_{10}H_{11}N_2O_2$ 191.08150 $[M+H]^+$ found 191.08165 $[M+H]^+$.

6.1.5. 2-(5-Methoxyfuro[3,2-b]pyridin-3-yl)acetonitrile (**6**)

o-Chloranil (242 mg, 1.0 mmol) was added to a solution of **5** (100 mg, 0.5 mmol) in toluene (7 mL). The mixture was stirred under reflux for 24 h. The media was allowed to warm to r.t. and was filtered through a silica pad rinsed with DCM. The filtrate was concentrated and the residue was purified by column chromatography (SiO_2, 95/5 petroleum ether/EtOAc) to afford **6** as a white solid. 30% of the starting material was recovered and engaged in a new aromatization reaction Yield: 55%; m.p.: 71–73 °C; IR (ATR Diamond, cm^{-1}) ν 2950, 2920, 2257, 1589, 1407, 1253, 1026; ^1H NMR (400 MHz, $CDCl_3$) δ 3.8 (s, 2H, H_{10}), 4.0 (s, 3H, OCH_3), 6.7 (d, 1H, $J = 9.0$ Hz, H_5), 7.7 (d, 1H, $J = 9.0$ Hz, H_4), 7.8 (s, 1H, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12 (CH_2), 54 (CH_3), 108 (CH), 112 (CN), 117 (Cq), 122 (CH), 142 (Cq), 145 (Cq), 146 (CH), 165 (Cq); HRMS (EI-MS): calculated for $C_{10}H_9N_2O_2$ 189.06585 $[M+H]^+$ found 189.06567 $[M+H]^+$.

6.1.6. N-(2-(5-Methoxyfuro[3,2-b]pyridin-3-yl)ethyl)acetamide (**7**)

In an autoclave, **6** (790 mg, 4.2 mmol) was dissolved in anhydride acetic (50 mL) and sodium acetate (520 mg, 6.3 mmol) and Raney nickel (cat.) were added. The mixture was stirred under hydrogen atmosphere (5 bars) at 60 °C for 24 h. The media was allowed to cool to r.t. and was filtered through a silica pad rinsed with EtOAc. Filtrate was washed with an aqueous solution of $NaHCO_3$. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed twice with distilled water, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (SiO_2, 8/2 petroleum ether/EtOAc) to afford **7** as a white solid. Yield: 60%; m.p.: 163–165 °C; IR (ATR Diamond, cm^{-1}) ν 3271, 3101, 2943, 1633, 1406, 1236, 1033; ^1H NMR (400 MHz, $CDCl_3$) δ 2.0 (s, 3H, CH_3), 2.9–3.0 (m, 2H, CH_2), 3.6–3.7 (m, 2H, CH_2), 4.0 (s, 3H, OCH_3), 6.7 (d, 1H, $J = 8.9$ Hz, H_5), 6.9 (bs, 1H, NH), 7.6 (s, 1H, H_2), 7.7 (d, 1H, $J = 8.9$ Hz, H_4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23 (CH_3), 24 (CH_2), 39 (CH_2), 54 (CH_3), 107 (CH), 118 (Cq), 121 (CH), 131 (Cq), 144 (Cq), 145.0 (Cq), 162 (Cq), 170 (Cq); HRMS (EI-MS): calculated for $C_{12}H_{14}N_2O_3$ 235.10772 $[M+H]^+$ found 235.10744 $[M+H]^+$. After analysis by high performance liquid chromatography (HPLC) the purity was found to be 82% and 87% at 254 nm and 323 nm, respectively.

6.1.7. N-(2-(2-Bromo-5-methoxyfuro[3,2-b]pyridin-3-yl)ethyl) acetamide (**8**)

Under argon, *n*-butyllithium (5 mL, 8.0 mmol) was added dropwise to a solution of **7** (190 mg, 0.8 mmol) in dry THF (10 mL) cooled to − 78 °C. The mixture was stirred at −78 °C for 1 h and a solution of carbon tetrabromide (400 mg, 1.6 mmol) in dry THF (5 mL) was added dropwise. The mixture was stirred at −78 °C for 1 h and was then quenched with water. This aqueous layer was extracted 3 times with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (SiO_2, 5/5 petroleum ether/EtOAc) to afford **8** as a white solid. Yield: 67%; m.p.: 139–141 °C; IR (ATR Diamond, cm^{-1}) ν 3282, 2919, 1635, 1569, 1402, 1258, 1230, 1122, 1020; ^1H NMR (400 MHz, $CDCl_3$) δ 2.0 (s, 3H, $COCH_3$), 2.9–3.0 (m, 2H, CH_2), 3.6–3.7 (m, 2H, CH_2), 4.0 (s, 3H, OCH_3), 6.7 (d, 1H, $J = 8.9$ Hz, H_5), 7.6 (d, 1H, $J = 8.9$ Hz, H_4); ^{13}C (100 MHz,$CDCl_3$) δ 23 (CH_3), 24 (CH_2), 39 (CH_2), 54 (CH_3), 107 (CH), 118 (Cq), 121 (CH), 131

(Cq), 144 (Cq), 145 (Cq), 162 (Cq), 170 (Cq); HRMS (EI-MS): calculated for $C_{12}H_{14}BrN_2O_3$ 313.01823 $[M+H]^+$ found 313.01828 $[M+H]^+$.

6.1.8. N-(2-(2-Iodo-5-methoxyfuro[3,2-b]pyridin-3-yl)ethyl) acetamide (**9**)

Under argon, *n*-butyllithium (5 mL, 8.0 mmol) was added dropwise to a solution of **7** (190 mg, 0.8 mmol) in dry THF (10 mL) cooled to − 78 °C. The mixture was stirred at −78 °C for 1 h and a solution of iodine (395 mg, 1.6 mmol) in dry THF (5 mL) was added dropwise. The mixture was stirred at −78 °C for 1 h and was then quenched with water. This aqueous layer was extracted 3 times with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (SiO_2, 5/5 petroleum ether/EtOAc) to afford **9** as a white cottony solid. Yield: 52%; m.p.: 170–172 °C; IR (ATR Diamond, cm^{-1}) ν 3276, 2945, 1627, 1583, 1434, 1231, 1100, 1028; ^1H NMR (400 MHz, $CDCl_3$) δ 1.9 (s, 3H, $COCH_3$), 2.8–2.9 (m, 2H, CH_2), 3.6–3.7 (m, 2H, CH_2), 4.0 (s, 3H, OCH_3), 6.6 (d, 1H, $J = 8.9$ Hz, H_5), 6.7 (bs, 1H, NH), 7.6 (d, 1H, $J = 8.9$ Hz, H_4); ^{13}C (100 MHz,$CDCl_3$) δ 24 (CH_3), 25 (CH_2), 39 (CH_2), 54 (CH_3), 102 (Cq), 107 (CH), 122 (CH), 126 (Cq), 143 (Cq), 148 (Cq), 162 (Cq), 170 (Cq); HRMS (EI-MS): calculated for $C_{12}H_{13}IN_2O_3$ 361.00437 $[M+H]^+$ found 361.00424 $[M+H]^+$. After analysis by HPLC, the purity was found to be 98.5% and 99% at 254 nm and 306 nm, respectively.

6.1.9. General procedure for the synthesis of 2-arylfuro[3,2-b] pyridines

Cesium carbonate (170 mg, 1.2 mmol) and arylboronic acid (0.3 mmol) were added to solution of **8** (70 mg, 0.2 mmol) in water (2 mL) and dioxane (5 mL). The mixture was degassed and tetrakis(triphenylphosphine)palladium (13 mg, 5 mol%) was added. The mixture was stirred under reflux for 4 h. The media was filtered over a silica pad rinsed with EtOAc and the filtrate was concentrated.

6.1.9.1. N-(2-(5-Methoxy-2-phenylfuro [3,2b]pyridin-3-yl)ethyl)acetamide (**10**).

Synthesized according to the general procedure using phenylboronic acid and purified by column chromatography (SiO_2, 5/5 petroleum ether/EtOAc) to afford **10** as a white solid. Yield: 90%; m.p.: 134–136 °C; IR (ATR Diamond, cm^{-1}) ν 3296, 2945, 1633, 1566, 1412, 1242, 1026; ^1H NMR (400 MHz, $CDCl_3$) δ 1.9 (s, 3H, CH_3), 3.1–3.2 (m, 2H, CH_2), 3.7–3.8 (m, 2H, CH_2), (s, 3H, CH_3), 6.7 (d, 1H, $J = 8.8$ Hz, H_4), 7.0 (bs, 1H, NH), 7.4–7.5 (m, 3H, H_{Ar}), 7.7 (d, 1H, $J = 8.8$ Hz, H_5), 7.7–7.8 (m, 2H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23 (CH_3), 23 (CH_2), 40 (CH_2), 54 (CH_3), 77 (CH), 107 (CH), 114 (Cq), 121(CH), 122 (CH), 126 (Cq), 127 (CH), 129 (CH), 129 (Cq), 131 (Cq), 144 (Cq), 146 (Cq), 162 (Cq), 170 (Cq); HRMS (EI-MS): calculated for $C_{18}H_{19}N_2O_3$ 311.13902 $[M+H]^+$ found 311.13945 $[M+H]^+$. After analysis by HPLC, the purity was found to be 90.4% and 99% at 254 nm and 304 nm, respectively.

6.1.9.2. N-(2-(2-(4-Fluorophenyl)5-methoxyfuro[3,2-b]pyridine-3-yl) ethyl)acetamide (**11**).

Synthesized according to the general procedure using 4-fluorophenylboronic acid and purified by column chromatography (SiO_2, 3/7 petroleum ether/EtOAc) to afford **11** as a white solid. Yield: 78%; m.p.: 160–162 °C; IR (ATR Diamond, cm^{-1}) ν 3279, 2947, 1610, 1414, 1248, 1230, 1023; ^1H NMR (400 MHz, $CDCl_3$) δ 1.9 (s, 3H, CH_3), 3.1–3.2 (m, 2H, CH_2), 3.7–3.8 (m, 2H, CH_2), 4.0 (s, 3H, CH_3), 6.7 (d, 1H, $J = 8.9$ Hz, H_4), 6.9 (bs, 1H, NH), 7.1–7.2 (m, 2H, H_{Ar}), 7.7 (d, 1H, $J = 8.9$ Hz, H_4), 7.7–7.8 (m, 2H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23 (CH_3), 27 (CH_2), 40 (CH_2), 54 (CH_3), 107 (CH), 114 (Cq), 116 (2xCH), 122 (CH), 127 (Cq), 129 (2xCH), 144 (Cq), 145 (Cq), 162 (Cq), 170 (Cq); HRMS (EI-MS): calculated for $C_{18}H_{18}FN_2O_3$ 329.12960 $[M+H]^+$ found 329.12934 $[M+H]^+$.

6.1.9.3. N-(2-(2-(2,6-Dimethylphenyl)-5-methoxyfuro[3,2-b]pyridin-3-yl)ethyl)acetamide (**12**).

Synthesized according to the general procedure using 2,6-dimethylphenylboronic acid and purified by column chromatography (SiO_2, 5/5 petroleum ether/EtOAc) to afford **12** as a pale yellow gum. Yield: 87%; IR (ATR Diamond, cm^{-1}) ν 3291, 2924, 1651, 1585, 1407, 1240,; ^1H NMR (400 MHz, $CDCl_3$) δ 1.9 (s, 3H, CH_3), 2.1 (s, 6H, 2xCH_3), 2.7–2.8 (m, 2H, CH_2), 3.5–3.6 (m, 2H, CH_2), 4.1 (s, 3H, CH_3), 6.7 (d, 1H, $J = 8.8$ Hz, H_5), 7.1 (d, 2H, $J = 8.8$ Hz, H_{Ar}), 7.2 (bs, 1H, NH), 7.2–7.3 (m, 1H, H_{Ar}), 7.7 (d, 1H, $J = 8.8$ Hz, H_4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20 (2xCH_3), 23 (CH_3), 23 (CH_2), 40 (CH_2), 54 (CH_3), 107 (CH), 116 (Cq), 122 (CH), 128 (2xCH), 129 (Cq), 130 (CH), 139 (2xCq), 144 (Cq), 144 (Cq), 156 (Cq), 162 (Cq), 170 (Cq); HRMS (EI-MS): calculated for $C_{20}H_{22}N_2O_3$ 339.17032 $[M+H]^+$ found 339.17020 $[M+H]^+$.

6.1.9.4. N-(2-(5-Methoxy-2-(naphthalen-1-yl)furo[3,2-b]pyridin-3-yl)ethyl)acetamide (**13**).

Synthesized according to the general procedure using 1-naphthylboronic acid and purified by column chromatography (SiO_2, 5/5 petroleum ether/EtOAc) to afford **13** as a white solid. Yield: 83%; m.p.: 117–119 °C; IR (ATR Diamond, cm^{-1}) ν 3241, 2932, 1631, 1585, 1418, 1239, 1053; ^1H NMR (400 MHz, $CDCl_3$) δ 1.8 (s, 3H, CH_3), 2.9–3.0 (m, 2H, CH_2), 3.5–3.6 (m, 2H, CH_2), 4.1 (s, 3H, CH_3), 6.8 (d, 1H, $J = 8.8$ Hz, H_5), 7.0 (bs, 1H, NH), 7.5–7.6 (m, 4H, H_{Ar}), 7.8 (d, 1H, $J = 8.8$ Hz, H_4), 7.7–7.8 (m, 1H, H_{Ar}), 7.9–8.0 (m, 2H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23 (CH_3), 23 (CH_2), 40 (CH_2), 54 (CH_3), 107 (CH), 117 (Cq), 122 (CH), 125 (CH), 126 (CH), 127 (CH), 127 (CH), 128 (CH), 129 (CH), 129 (CH), 131 (CH), 132 (Cq), 134 (Cq), 144 (Cq), 145 (Cq), 156 (Cq), 162 (Cq), 170 (Cq); HRMS (EI-MS): calculated for $C_{22}H_{20}N_2O_3$ 361.15467 $[M+H]^+$ found 361.15484 $[M+H]^+$. After analysis by HPLC, the purity was found to be 99% and 99.1% at 254 nm and 315 nm, respectively.

6.1.9.5. N-(2-(5-Methoxy-2-(naphthalen-2-yl)furo[3,2-b]pyridin-3-yl)ethyl)acetamide (**14**).

Synthesized according to the general procedure using 2-naphthylboronic acid and purified by column chromatography (SiO_2, 5/5 petroleum ether/EtOAc) to afford **14** as a white solid. Yield: 60%; m.p.: 112–114 °C; IR (ATR Diamond, cm^{-1}) ν 3281, 2926, 1633, 1412, 1245, 1026; ^1H NMR (400 MHz, $CDCl_3$) δ 1.9 (s, 3H, CH_3), 3.2–3.3 (m, 2H, CH_2), 3.7–3.8 (m, 2H, CH_2), 3.8 (s, 3H, CH_3), 6.7 (d, 1H, $J = 8.8$ Hz, H_5), 7.0 (bs, 1H, NH), 7.5–7.6 (m, 2H, H_{Ar}), 7.7 (d, 1H, $J = 8.8$ Hz, H_4), 7.9–8.0 (m, 4H, H_{Ar}), 8.3 (s, 1H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23 (CH_3), 24 (CH_2), 40 (CH_2), 54 (CH_3), 107 (CH), 115 (Cq), 122 (CH), 124 (CH), 127 (CH), 127 (CH), 127 (CH), 128 (CH), 128 (Cq), 129 (CH), 129 (CH), 133 (Cq), 133 (Cq), 144 (Cq), 146 (Cq), 155 (Cq), 162 (Cq), 170 (Cq); HRMS (EI-MS): calculated for $C_{22}H_{20}N_2O_3$ 361.15467 $[M+H]^+$ found 361.15487 $[M+H]^+$. After analysis by HPLC, the purity was found to be 98.6% at 336 nm.

6.1.9.6. N-(2-(2-(Anthracen-9-yl)-5-methoxyfuro[3,2-b]pyridin-3-yl) ethyl)acetamide (**15**).

Synthesized according to the general procedure using 9-anthraceneboronic acid and purified by column chromatography (SiO_2, 5/5 petroleum ether/EtOAc) to afford **15** as a white solid. Yield: 80%; m.p.: 117–119 °C; IR (ATR Diamond, cm^{-1}) ν 3338, 2923, 1672, 1533, 1242, 1022; ^1H NMR (400 MHz, $CDCl_3$) δ 1.8 (s, 3H, CH_3), 2.9–3.0 (m, 2H, CH_2), 3.6–3.7 (m, 2H, CH_2), 4.1 (s, 3H, CH_3), 6.8 (d, 1H, $J = 8.9$ Hz, H_5), 7.0 (bs, 1H, NH), 7.6–7.8 (m, 5H, H_{Ar}), 7.8 (d, 1H, $J = 8.9$ Hz, H_4), 7.9 (d, 1H, $J =$ Hz, H_{Ar}), 7.9 (s, 1H, H_{Ar}), 8.0 (d, 1H, $J =$ Hz, H_{Ar}), 8.7–8.8 (m, 2H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23 (CH_3), 24 (CH_2), 40 (CH_2), 54 (CH_3), 108 (CH), 117 (Cq), 122 (CH), 123 (CH), 123 (CH), 126 (CH), 127 (Cq), 127 (CH), 127 (CH), 127 (CH), 128 (CH), 129 (CH), 131 (CH), 131 (Cq), 131 (Cq), 131(Cq), 131(Cq), 144 (Cq), 145 (Cq), 156 (Cq), 162 (Cq), 170 (Cq); HRMS (EI-MS): calculated for $C_{26}H_{23}N_2O_3$ 411.17032 $[M+H]^+$ found 411.017049 $[M+H]^+$. After analysis by HPLC, the purity was found to be 95.4% and 96.7% at 254 nm and 302 nm, respectively.

*6.1.9.7. N-(2-(5-Methoxy-2-(phenanthren-9-yl)furo[3,2-b]pyridine-3-yl)ethyl)acetamide (**16**).* Synthesized according to the general procedure using 9-phenanthreneboronic acid and purified by column chromatography (SiO_2, 5/5 petroleum ether/EtOAc) to afford **16** as a white solid. Yield: 95%; m.p.:167–169 °C; IR (ATR Diamond, cm^{-1}) ν 3248, 3078, 2939, 1636, 1440, 1404, 1241, 1027; ^1H NMR (400 MHz, $CDCl_3$) δ 1.7 (s, 3H, CH_3), 2.7–2.8 (m, 2H, CH_2), 3.4–3.5 (m, 2H, CH_2), 4.1 (s, 3H, CH_3), 6.7 (bs, 1H, NH), 6.8 (d, 1H, $J = 8.9$ Hz, H_5), 7.4–7.5; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23 (CH_3), 24 (CH_2), 40 (CH_2), 54 (CH_3), 108 (CH), 119 (Cq), 122 (CH), 123 (Cq), 125 (2xCH), 126 (2xCH), 127 (2xCH), 129 (2xCH), 130 (CH), 131 (2xCq), 132 (2xCq), 144 (Cq), 145 (Cq), 154 (Cq), 162 (Cq), 170 (Cq); HRMS (EI-MS): calculated for $C_{26}H_{23}N_2O_3$ 411.17032 $[M+H]^+$ found 411.17065 $[M+H]^+$. After analysis by HPLC, the purity was found to be 99.6% and 98.7% at 254 nm and 314 nm, respectively.

6.1.10. Control of purity by high performance liquid chromatography (HPLC) followed by UV-DAD detection

Purifications of prepared compounds were performed on a liquid chromatography system equipped with a Diode Array Detector (DAD) (Agilent). Samples were injected on a Kinetex C18 (Phenomenex) column, 2.1 mm diameter, 150 mm length and 1.7 μm particle size. . The mobile phase consisted of 70%/30% methanol/water (v/v) and with 0.1% formic acid. The determination of the purity was performed in isocratic mode for compounds **10**, **15**, and **16**. A gradient with a 70%/30% concentration of methanol/water with 0.1% formic acid and reaching 100% methanol with 0.1% formic acid in 20 min was used for the determination of purity of compounds **7**, **9**, **13**, and **14**. Except for compound **14**, the purity was determined at two wavelengths. The chosen wavelengths correspond to the absorption maxima observed on the UV spectrum.

6.2. Biological assays

2-[^{125}I]-iodomelatonin binding assay conditions were essentially as previously described [37]. Briefly, binding was initiated by addition of membrane preparations from stable transfected HEK cells (4 μg/mL) diluted in binding buffer (50 mM Tis HCl buffer, pH 7.4 containing 5 mM $MgCl_2$) to 2-[^{125}I]-iodomelatonin (0.025 and 0.2 nM respectively for MT_1 and MT_2 receptors due to a MT_1/MT_2 ratio of approximately 0.125 for cold 2-iodomelatonin) and the tested drug. Nonspecific binding was defined in the presence of 1 μM melatonin. After a 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 analyzed using the program PRISM (Graph Pad Software Inc., San Diego, CA, USA) 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 [38]. Briefly, membranes from transfected CHO celles and compounds were dilutes 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 antagonist on MT_2 receptors, membranes were preincubated with both the melatonin (3 mM) and the antagonist for 30 min prior to the addition of [^{35}S] GTPγS. Nonspecific 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 respectively for CHO-MT_1 and CHO-MT_2 membranes 1000 and 2000 for basal activity, 4800 and 8000 in the presence of melatonin 1 μM and 160 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 analyzed by using the program PRISM (Graph Pad Software Inc., San Diego, CA, USA) 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} agi is the EC_{50} of the molecule when tested alone.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2016.01.008.

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