# Synthesis and Structure−Affinity−Activity Relationships of Novel Benzofuran Derivatives as $MT_2$ Melatonin Receptor Selective Ligands

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A series of *N*-(2-phenylbenzofuran-3-yl) ethyl amide and *N*-(2-arylalkylbenzofuran-3-yl) ethyl amide derivatives were synthesized and evaluated as melatonin receptor ligands. The affinity of each compound for the two $MT_1$ and $MT_2$ melatonin receptor subtypes was determined by binding studies using 2-[$^{125}$I]iodomelatonin on human embryonic kidney cell line HEK293 membrane homogenates. The intrinsic activity of the most interesting compounds was evaluated on the [$^{35}$S]GTP$\gamma$S binding assay. Introduction of a 2-phenyl substituent in the C-2 benzofuran position leads to an agonist compound, **10q**, which binds more strongly than melatonin itself to both $MT_1$ and $MT_2$ subtypes. On the other hand, a 2-benzyl group in the same position allows $MT_2$ antagonist selective ligands to be obtained. The $MT_2$ selectivity and antagonist potency can be modulated with suitable modifications on the *N*-acyl and benzyl substituents, and the most selective compounds **10c** and **19** show affinity ratios of 123 and 192, respectively, and bind to the $MT_2$ subtype similarly to melatonin itself (0.1 nM). Nevertheless, **10c** acts as an $MT_1$ and $MT_2$ antagonist, whereas **19** is a partial agonist.

## Introduction

Melatonin (5-methoxy-*N*-acetyltryptamine) (**1a**) (Chart 1) is a neurohormone synthesized in the pineal gland during the dark period whatever the species considered including humans.[1] Synthesis of melatonin is regulated by circadian and seasonal variations in day length. Melatonin acts through the blood circulation as an internal synchronizer of circadian rhythms. The central and peripheral structures, which represent melatonin receptors or binding sites, receive the information about the photoperiod.

Two human melatonin receptors have been cloned[2,3] and defined as $MT_1$ and $MT_2$ receptors.[4] These two receptors belong to the family of seven-transmembrane-domain G-protein-coupled receptors. Both receptors have similar binding for melatonin and display similar rank orders for the binding of reference melatonin ligands despite 60% homology between the two receptors. Activation of these two receptor subtypes leads to the inhibition of adenylyl cyclase probably through activation of a Gi protein.[2,3] The studies of their tissue distribution[2,3] in mammals show that these receptors are localized in different areas of the brain (suprachiasmatic nucleus, pars tuberalis, hypothalamus, cerebellum, cortex, hippocampus, cerebral vessels) and at the peripheral level in the kidney, small intestine, and caudal arteries.[2−9] From these studies, it appears that the two receptors are colocalized in the hippocampus and suprachiasmatic nucleus. This diversity and the differences in tissue distribution are in favor of different functional roles for each receptor subtype. Pharmacological investigations with selective agonist or antagonist ligands are therefore necessary to determine the physiological role of these melatonin receptor subtypes and their implication in physiopathological processes. This information will probably open new therapeutic perspectives for selective ligands, different from the chronobiotic properties of melatonin clearly demonstrated in humans.[10,11]

**Chart 1**

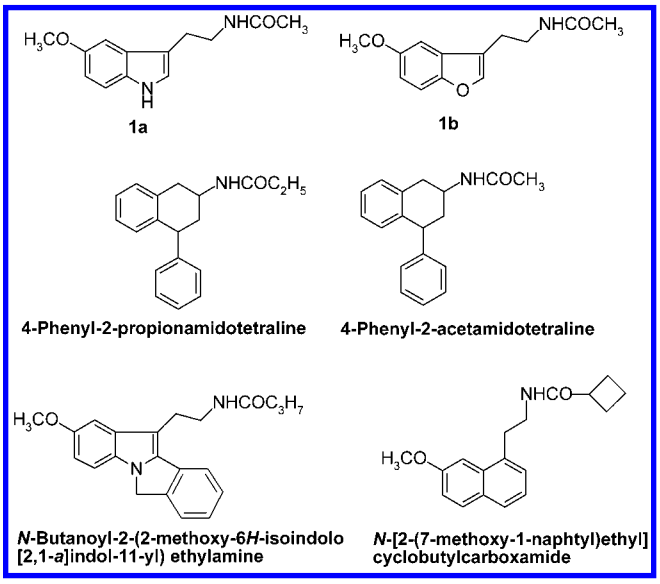


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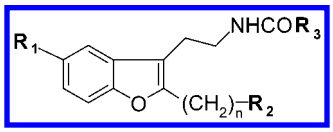
**Table 1.** $MT_1$ and $MT_2$ Receptor Binding Affinities of Benzofuran Compounds



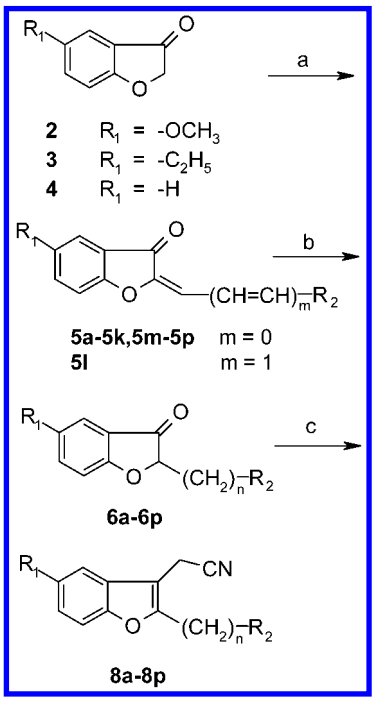

| compd | *n* | $R_1$ | $R_2$ | $R_3$ | $K_i \pm$ SEM (nM) ($MT_1$) | $K_i \pm$ SEM (nM) ($MT_2$) | $MT_1/MT_2$ |
|---|---|---|---|---|---|---|---|
| **1a** | | | | | 0.12 ± 0.02 | 0.31 ± 0.05 | 0.4 |
| **1b** | 0 | −OCH3 | −H | $-CH_3$ | 0.15 ± 0.02 | 0.34 ± 0.02 | 0.5 |
| **10a** | 1 | $-OCH_3$ | $-C_6H_5$ | $-CH_3$ | 1.27 ± 0.02 | 0.05 ± 0.02 | 23 |
| **10b** | 1 | $-OCH_3$ | $-C_6H_4(OCH_3)$ (*o*) | $-CH_3$ | 14.3 ± 2.00 | 0.34 ± 0.03 | 42 |
| **10c** | 1 | $-OCH_3$ | $-C_6H_4(OCH_3)$ (*m*) | $-CH_3$ | 40.6 ± 1.70 | 0.32 ± 0.09 | 123 |
| **10d** | 1 | $-OCH_3$ | $-C_6H_4(OCH_3)$ (*p*) | $-CH_3$ | 24.0 ± 3.50 | 0.50 ± 0.20 | 48 |
| **10e** | 1 | $-OCH_3$ | $-C_6H_4(F)$ (*m*) | $-CH_3$ | 0.75 ± 0.10 | 0.23 ± 0.08 | 2.8 |
| **10f** | 1 | $-OCH_3$ | $-C_6H_4(CF_3)$ (*m*) | $-CH_3$ | 80.0 ± 28.7 | 1.17 ± 0.34 | 69 |
| **10g** | 1 | $-OCH_3$ | $-C_6H_4(Cl)$ (*m*) | $-CH_3$ | 7.19 ± 1.92 | 0.22 ± 0.01 | 33 |
| **10h** | 1 | $-OCH_3$ | $-C_6H_3(Cl)_2$ (*o, o*) | $-CH_3$ | 84.5 ± 0.01 | 12.8 ± 1.90 | 6.6 |
| **10i** | 1 | $-OCH_3$ | $-C_6H_3(CF_3)_2$ (*m, m*) | $-CH_3$ | 476 ± 53.0 | 340 ± 24.0 | 1.4 |
| **10j** | 1 | $-OCH_3$ | $-C_6H_{11}$ | $-CH_3$ | 66.4 ± 3.10 | 2.49 ± 1.05 | 27 |
| **10k** | 1 | $-OCH_3$ | $-C_5H_4N$ (*m*) | $-CH_3$ | 29.0 ± 2.00 | 3.53 ± 1.14 | 8.2 |
| **10l** | 3 | $-OCH_3$ | $-C_6H_5$ | $-CH_3$ | 31.5 ± 6.10 | 1.52 ± 0.56 | 21 |
| **10m** | 1 | $-C_2H_5$ | $-C_6H_5$ | $-CH_3$ | 64.4 ± 15.7 | 8.25 ± 0.88 | 7.8 |
| **10n** | 1 | $-C_2H_5$ | $-C_6H_4(OCH_3)$ (*m*) | $-CH_3$ | 288 ± 21.0 | 17.0 ± 6.70 | 17 |
| **10o** | 1 | −H | $-C_6H_5$ | $-CH_3$ | 155 ± 14.0 | 10.6 ± 1.30 | 15 |
| **10p** | 1 | −H | $-C_6H_4(OCH_3)$ (*m*) | $-CH_3$ | 229 ± 2.00 | 18.6 ± 3.00 | 12 |
| **10q** | 0 | $-OCH_3$ | $-C_6H_5$ | $-CH_3$ | 0.01 ± 0.01 | 0.02 ± 0.01 | 0.7 |
| **11** | 1 | $-OCH_3$ | $-C_6H_5$ | $-CH_2I$ | 8.67 ± 3.43 | 0.41 ± 0.04 | 21 |
| **12** | 1 | $-OCH_3$ | $-C_6H_5$ | $-C_3H_7$ | 3.29 ± 0.43 | 0.20 ± 0.10 | 17 |
| **13** | 1 | $-OCH_3$ | $-C_6H_5$ | −furyl | 698 ± 12.0 | 36.7 ± 1.80 | 19 |
| **14** | 1 | $-OCH_3$ | $-C_6H_5$ | $-CH{=}CH_2$ | 53.7 ± 12.0 | 0.69 ± 0.14 | 78 |
| **15** | 1 | $-OCH_3$ | $-C_6H_4(OCH_3)$ (*m*) | $-CH{=}CH_2$ | 55.0 ± 15.2 | 2.76 ± 0.57 | 20 |
| **16** | 0 | $-OCH_3$ | $-C_6H_5$ | $-CH{=}CH_2$ | 0.02 ± 0.01 | 0.01 ± 0.01 | 1.5 |
| **17** | 0 | $-OCH_3$ | $-C_6H_5$ | −furyl | 12.9 ± 1.50 | 1.70 ± 0.10 | 7.6 |
| **18** | 1 | $-OCH_3$ | $-C_6H_5$ | $-CH_2CH{=}CH_2$ | 3.51 ± 2.30 | 0.06 ± 0.03 | 57 |
| **19** | 1 | $-OCH_3$ | $-C_6H_4(OCH_3)$ (*m*) | $-CH_2CH{=}CH_2$ | 21.6 ± 2.50 | 0.11 ± 0.02 | 192 |
| **20** | 0 | $-OCH_3$ | $-C_6H_5$ | $-CH_2CH{=}CH_2$ | 0.01 ± 0.01 | 0.02 ± 0.01 | 0.7 |
| **21** | 0 | $-OCH_3$ | $-C_6H_5$ | $-CH{=}CHCH_3$ | 1.01 ± 0.32 | 0.21 ± 0.02 | 4.8 |
| **22** | 1 | $-OCH_3$ | $-C_6H_5$ | $-NHCH_3$ | 5.37 ± 0.16 | 0.35 ± 0.01 | 15 |
| **23** | 0 | $-OCH_3$ | $-C_6H_5$ | $-NHCH_3$ | 0.04 ± 0.01 | 0.04 ± 0.01 | 1.2 |
| **24** | 1 | −OH | $-C_6H_5$ | $-CH_3$ | 569 ± 90.0 | 79.9 ± 9.10 | 7.1 |
| **25** | 1 | $-OC_5H_{11}$ | $-C_6H_5$ | $-CH_3$ | 42.7 ± 5.50 | 9.64 ± 1.16 | 4.4 |
| **26** | 1 | $-OC_6H_{13}$ | $-C_6H_5$ | $-CH_3$ | 8.20 ± 2.31 | 3.21 ± 0.22 | 2.6 |

The first $MT_2$ selective antagonists 4-phenyl-2-propionamidotetraline and 4-phenyl-2-acetamidotetraline (Chart 1) were reported in 1997 with $MT_1/MT_2$ affinity ratios of about 300.[12] These new pharmacological tools have recently led to the identification of functional $MT_2$ receptors in the suprachiasmatic nucleus, retina, and rat caudal artery, respectively, involved in the resynchronization of circadian rhythms,[13] inhibition of dopamine release,[12] and vasodilatation.[14] Selective $MT_2$ agonists *N*-butanoyl-2-(2-methoxy-6*H*-isoindolo[2,1-*a*]-indol-11-yl) ethylamine and (*N*-[2-(7-methoxy-1-naphthyl)ethyl] cyclobutylcarboxamide (Chart 1) have also been reported[15,16] with $MT_1/MT_2$ affinity ratios of about 80. To date there is no selective agonist or antagonist for the $MT_1$ receptor.

The synthesis of selective melatonin receptor ligands is still a challenge. During the past decade, the synthesis and biological study of potent indole and non-indole melatonin receptor ligands have improved our knowledge of the structural requirements for the binding of melatonin to its receptors: the key elements for high binding affinity are the presence and the relative spatial position of the methoxy group and the *N*-alkylamido side chain linked to an appropriate spacer.[17−19] The proton donor NH indole is not essential, and several potent ligands have been designed on the basis of their bioisosterism with the indole heterocycle such as the naphthalene, benzothiophene, and benzofuran analogues. Unfortunately most literature binding data have been obtained from tissues expressing more than one receptor subtype, and it is quite impossible to define structure−affinity relationships for the different receptor subtypes with the available binding data.

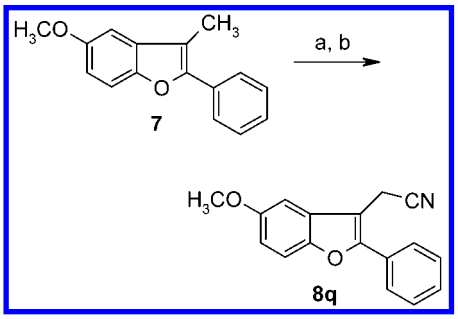
Here, we report the synthesis of new benzofuran compounds and their binding characteristics on the human $MT_1$ and $MT_2$ melatonin receptors. The benzofuran ring was selected for chemical modifications as it has been reported that benzofuran analogues of melatonin, such as *N*-acetyl-2-(5-methoxybenzo[*b*]furan-3-yl) ethylamine (**1b**) (Chart 1 and Table 1), are good ligands for the melatonin receptors,[20] and are metabolically more stable than melatonin.[21] Different arylalkyl groups, a cyclohexylmethyl and a phenyl, were introduced on the 2 position of the benzofuran bioisostere (Table 1) to modify the intrinsic activity, the affinity toward the two receptor subtypes $MT_1$ and $MT_2$, and so the selectivity. With this aim and to confirm the role of the *N*-acyl side chain and the 5-methoxy group on the binding affinity and the intrinsic activity, modifications were also made to these two substituents (Table 1). For all these compounds, the synthesis, the binding data, and some activity results for the human $MT_1$ and $MT_2$ melatonin receptors are reported.

**Scheme 1**[a]




[a] Reagents: (a) $R_2(CH{=}CH)_mCHO$, $Al_2O_3$, methylene chloride; (b) $H_2$, Pd/C, methanol, dioxane; (c) NaH, $(EtO)_2POCH_2CN$, HMPT, anhydrous THF.

**Scheme 2**[a]




[a] Reagents: (a) NBS, AIBN, $CCl_4$; (b) NaCN, DMSO.

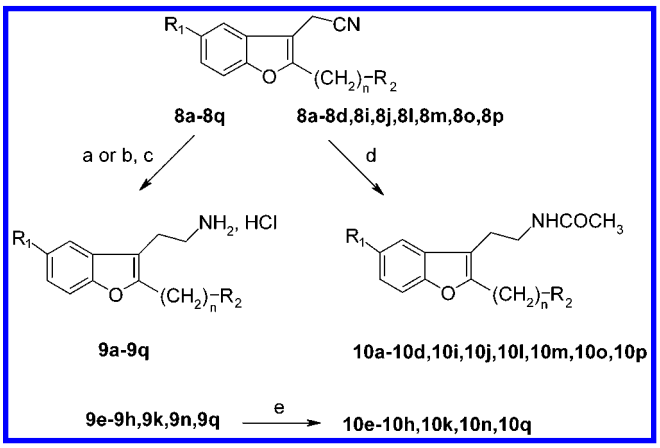
## Chemistry

Key intermediates in the synthesis of the target compounds **10a**−**10q** and **11**−**24** are the corresponding acetonitriles **8a**−**8q** (Schemes 1 and 2) and the primary amines **9a**−**9q** (Schemes 3 and 4).

The nitriles **8a**−**8p** (Scheme 1) were prepared from the previously described[22,23] 5-methoxy- or 5-ethyl-3-oxo-2,3-dihydrobenzo[*b*]furans (**2, 3**) and the commercially available 3-oxo-2,3-dihydrobenzo[*b*]furan (**4**). Compounds **2**−**4** reacted with the appropriate aldehydes in methylene chloride in the presence of aluminum oxide as solid support[24] to afford the corresponding α,*β*-unsaturated ketones **5a**−**5p**, which were hydrogenated in methanol and dioxane with Pd/C as catalyst. A Horner−Emmons reaction on the resulting ketones **6a**−**6p** with the carbanion formed in situ by sodium hydride and the diethyl cyanomethylphosphonate as reactant[25] in HMPT[26] and tetrahydrofuran gave then the desired nitriles **8a**−**8p**.

To obtain the nitrile **8q** (Scheme 2), the previously described[27,28] 5-methoxy-3-methyl-2-phenylbenzo[*b*]furan (**7**) was first brominated with *N*-bromosuccinimide in the presence of AIBN in $CCl_4$, and the resulting bromo intermediate, which was not isolated, was substituted with sodium cyanide in DMSO.

**Scheme 3**[a]




[a] Reagents: (a) $H_2$, Raney nickel, ethanol; (b) $BH_3$, THF; (c) HCl, ether; (d) $H_2$, Raney nickel, $(CH_3CO)_2O$; (e) $CH_3COCl$, $K_2CO_3$, $H_2O$, methylene chloride.

The primary amines **9a**−**9q** were prepared from the nitriles **8a**−**8q** by hydrogenation in the presence of Raney nickel as catalyst in ethanol or by reduction with a borane−tetrahydrofuran complex, and isolated in the form of hydrochloride salts by treatment with HCl gas in ether (Scheme 3). The *N*-acetyl derivatives **10a**−**10q** were then prepared through two methods of synthesis (Scheme 3): by hydrogenation of the nitriles **8a**−**8d, 8i, 8j, 8l, 8m, 8o,** and **8p** in the presence of Raney nickel as catalyst in acetic anhydride or from the amine hydrochlorides **9e**−**9h, 9k, 9n,** and **9q** in a biphasic medium (according to a variant of the Schotten−Baumann procedure[29]) by treatment with the acetyl chloride in the presence of $K_2CO_3$ as base.

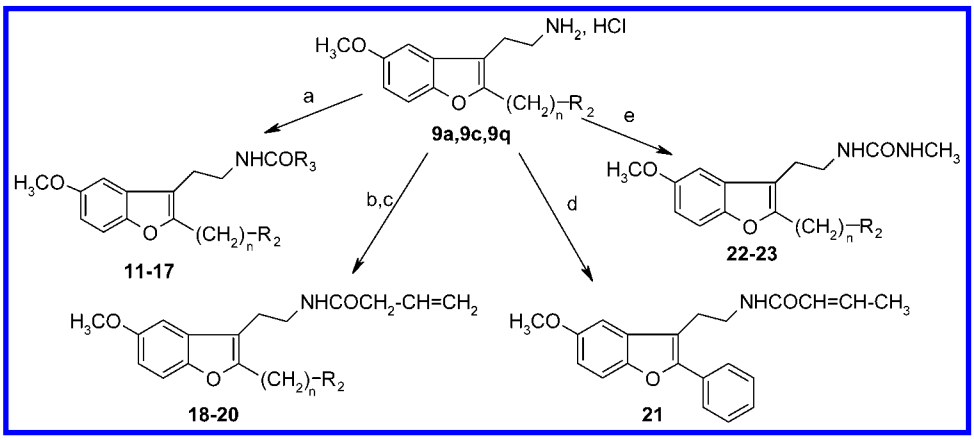
By using this last reaction with the appropriate acid chlorides, the amine hydrochlorides **9a, 9c,** and **9q** led to the *N*-acylated compounds **11**−**17** (Scheme 4). A peptide coupling reaction type in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbidiimide hydrochloride (EDCI) between the amine hydrochlorides **9a, 9c,** and **9q**, liberated from the hydrochloride by washing with a solution of $K_2CO_3$ and extracting with ether, and vinylacetic acid gave the amides **18**−**20** (Scheme 4). This reaction was made again between the amine hydrochloride **9q** and the vinylacetic acid, but with addition of triethylamine and 1-hydroxybenzotriazole hydrate (HOBt) in the mixture (Scheme 4). An isomerization of the unsaturated bond was then observed thanks to the $^1H$ NMR studies, and the amide **21** was isolated. The ureas **22** and **23** were finally obtained from the amine hydrochlorides **9a** and **9q** by reaction of methylisocyanate in pyridine (Scheme 4).

Treatment of amide **10a** with the $BBr_3/Me_2S$ complex gave the hydroxy compound[30] **24**, which then reacted with the appropriate alkyl iodide in the presence of $K_2CO_3$ as base to afford the corresponding ethers **25** and **26** (Scheme 5).

## Pharmacology

The compounds were evaluated for their binding affinity for human $MT_1$ and $MT_2$ receptors stably transfected in human embryonic kidney (HEK 293) cells, using 2-[$^{125}$I]iodomelatonin as radioligand.

**Scheme 4**[a]

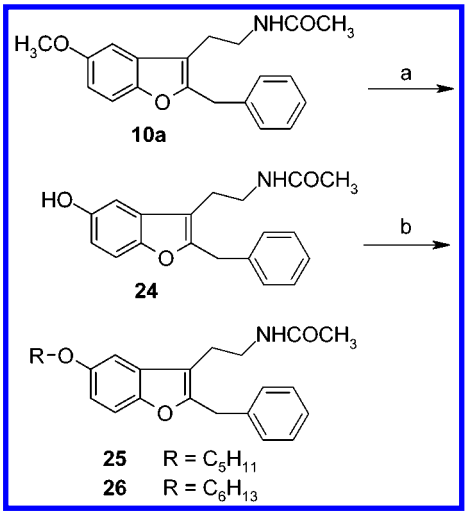



[a] Reagents: (a) $R_3COCl$, $K_2CO_3$, $H_2O$, methylene chloride; (b) $K_2CO_3$, water, ether; (c) $CH_2$=$CHCH_2COOH$, EDCI, methylene chloride; (d) $CH_2$=$CHCH_2COOH$, EDCI, $Et_3N$, HOBt, methylene chloride; (e) $CH_3NCO$, pyridine.

**Table 2.** Intrinsic Activity Values

| | $MT_1$ | | | $MT_2$ | | |
|---|---|---|---|---|---|---|
| compd | $EC_{50}$ ± SEM (nM) | $E_{max}$ ± SEM (%) | $K_B$ ± SEM (nM) | $EC_{50}$ ± SEM (nM) | $E_{max}$ ± SEM (%) | $K_B$ ± SEM (nM) |
| **1a** | 1.92 ± 0.38 | 100 | ND | 0.47 ± 0.07 | 100 | ND |
| **10a** | 21 ± 4 | 48 ± 6 | ND | >10000 | <10 | 0.21 ± 0.04 |
| **10b** | >10000 | <10 | 26 ± 6 | 0.41 ± 0.18 | 25 ± 1 | 0.88 ± 0.45 |
| **10c** | 37 ± 21 | 25 ± 11 | 26 ± 5 | 0.72 ± 0.13 | 30 ± 1 | 1.65 ± 0.44 |
| **10d** | >10000 | <10 | 35 ± 8 | >10000 | <10 | 0.42 ± 12 |
| **10f** | >10000 | <10 | 89 ± 10 | 1.26 ± 0.53 | 13 ± 1 | 2.4 ± 0.71 |
| **10j** | 481 ± 63 | 41 ± 10 | 242.4 ± 116 | 10 ± 3 | 41 ± 4 | 7 ± 1 |
| **10n** | >10000 | <10 | 266 ± 50 | 19 ± 9 | 25 ± 2 | 18 ± 2 |
| **10o** | >10000 | <10 | 27 ± 9 | >10000 | <10 | 12 ± 3 |
| **10q** | 0.17 ± 0.05 | 100 ± 5 | ND | 0.096 ± 0.001 | 100 ± 1 | ND |
| **18** | 25 ± 5 | 35 ± 3 | ND | 0.17 ± 0.06 | 20 ± 3 | 0.16 ± 0.06 |
| **19** | 138 ± 11 | 43 ± 9 | 57 ± 17 | 0.39 ± 0.04 | 44 ± 1 | 0.24 ± 0.02 |

**Scheme 5**[a]




[a] Reagents: (a) $BBr_3/Me_2S$, methylene chloride; (b) R−I, $K_2CO_3$, acetonitrile.

The activity and efficacy of the most interesting compounds were evaluated on [$^{35}$S]guanosine-5′-*O*-(3-thiotriphosphate) ([$^{35}$S]GTP$\gamma$S) binding in Chinese hamster ovarian (CHO) cells, stably transfected with human $MT_1$ and $MT_2$ receptors. This test measures the interaction between the melatonin receptors and the G proteins.

An agonist stimulates [$^{35}$S]GTP$\gamma$S binding, and this stimulation is proportional to the efficacy and intrinsic activity of the molecule. By convention, the natural ligand melatonin has an efficacy ($E_{max}$) of 100%. Full agonists stimulate [$^{35}$S]GTP$\gamma$S binding with a maximum efficacy, close to that of melatonin itself. If $E_{max}$ is between 30% and 70%, the compound is considered a partial agonist. Whereas if $E_{max}$ is inferior to 30%, the compound is considered an antagonist. In this last case the antagonist potency ($K_B$) is determined against 30 or 3 nM melatonin for $MT_1$ or $MT_2$, respectively.

## Results and Discussion

The chemical structures, binding affinities, and $MT_1$/$MT_2$ selectivity ratios of the new compounds are reported in Table 1. The intrinsic activities of the most interesting ones are shown in Table 2.

The benzofuran bioisostere of melatonin (**1b**) can be considered a very interesting lead compound: (i) its affinity values for both $MT_1$ and $MT_2$ receptors are nearly the same as those of melatonin (Table 1), and (ii) its predicted bioavailability is different and better than that of melatonin.[21]

Starting from this benzofuran bioisostere, we decided to incorporate changes at the C-2 and C-5 positions and in the acyl side chain to investigate structure−affinity (selectivity) and structure−activity relationships for $MT_1$ and $MT_2$ subtypes.

(**a) 2-Phenylbenzofurans.** The positive effect of a 2-phenyl substitution already described for melatonin itself and some analogues in displacing 2-[$^{125}$I]iodomelatonin from different tissues[31,32] is also observed in our series and affects both $MT_1$ and $MT_2$ subtypes,

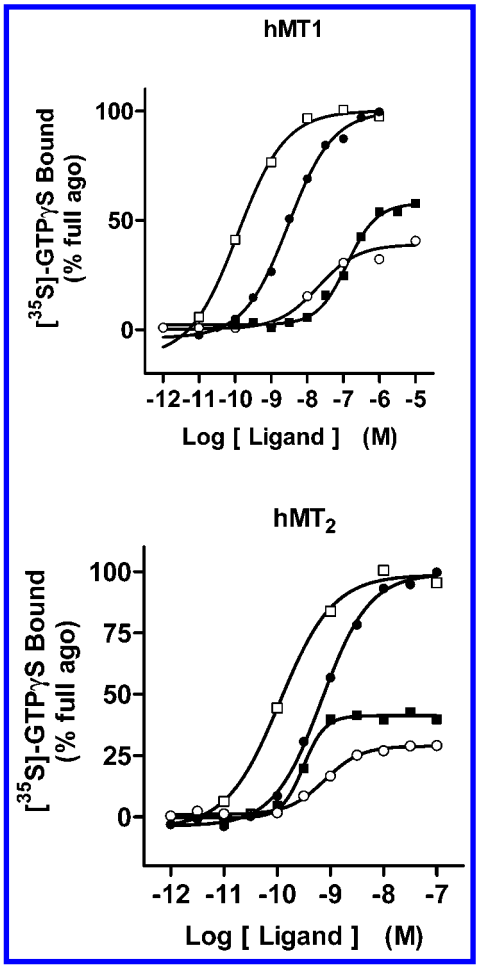



**Figure 1.** Comparison of the [$^{35}$ S]GTP$\gamma$S binding curves of **1a** (●), **10q** (□), **10c** (○), and **19** (■) tested on hMT$_1$ and hMT$_2$ expressed in CHO cells. Agonist stimulation of [$^{35}$ S]GTP$\gamma$S binding (0.1 nM) is expressed as the percentage of basal binding taken at 0% in the presence of various logarithmic concentrations of ligands (1 pM to 0.1 $\mu$M).

leading to one of the most potent agonist melatonin receptor ligands reported to date (**10q**; Figure 1). This result is in agreement with previous studies concerning the indole series[31,32] and confirms the hypothesis of a secondary binding site around the C-2 position, but it also allows the specification that this secondary binding site is present in both MT$_1$ and MT$_2$ receptor subtypes. Structural variations at the *N*-alkylamido group were found to be less important than in other series of melatonin analogues.[20,33] Replacement of the methyl group of the amide side chain by a vinyl (**16**), allyl (**20**), or methylamino (**23**) does not modify the binding affinity for each of the two receptor subtypes, all these compounds therefore being devoid of selectivity. Nevertheless, methylvinyl (**21**) and furyl (**17**) substituents decrease the binding affinity for MT$_1$ more than for MT$_2$.

(**b) 2-Benzylbenzofurans.** Introduction of a benzyl group in the C-2 benzofuran position (**10a**) slightly increases the MT$_2$ binding affinity but decreases the MT$_1$ binding affinity 10-fold, leading to a quite interesting selectivity ratio (MT$_1$/MT$_2$ = 23). Moreover, this compound behaves as an MT$_2$ antagonist and an MT$_1$ partial agonist. We therefore decided to select this compound (**10a**) as a lead in the search for MT$_2$ selective agents.

(**i) Variations of the 2-Benzyl Group.** The presence of various substituents on the 2-benzyl moiety allows the MT$_2$ selectivity to be modulated. This selectivity is better for the compounds bearing a methoxy group (**10b**−**10d**) than for the unsubstituted derivative (**10a**). Moreover, it depends on the position of this group on the aromatic ring, the meta position being the most favorable: compound **10c** (MT$_1$/MT$_2$ ratio 123) is about 5-fold more selective for MT$_2$ than the lead **10a** and 3-fold more selective than its isomers **10b** and **10d**. Moreover, this selective compound presents an affinity for MT$_2$ similar to that of melatonin itself and acts as an MT$_2$ and MT$_1$ antagonist (Figure 1). Replacement of the methoxy group on the meta position by a trifluoromethyl (**10f**) or a chlorine (**10g**) decreases the MT$_2$ selectivity, which totally disappears with the fluoro derivative (**10e**). On the other hand, introduction of two substituents on the aromatic ring in the ortho (**10h**) or meta (**10i**) position is particularly unfavorable for both affinity and selectivity. All these results show that steric and electronic parameters are probably involved in the influence of the 2-benzyl moiety on affinity and selectivity. Replacement of the phenyl group by a pyridin-3-yl heterocycle (**10k**) decreases the MT$_2$ affinity more strongly than the MT$_1$ affinity and therefore the selectivity, whereas lengthening the side chain from one to three methylene groups (**10l**) leads to the same selectivity ratio as that for the phenyl but with a decrease in binding affinity. The substitution of the aromatic phenyl ring in the 2 position with a cyclohexyl group (**10j**) causes a decrease in both MT$_1$ and MT$_2$ binding affinities and a partial loss of the antagonist potency; compound **10j** acts as a partial agonist with an MT$_2$ selectivity ratio of 27.

These results confirm the previously reported hypothesis that both MT$_1$ and MT$_2$ subtypes possess a secondary binding site around the C-2 position.[34] This binding site could be a hydrophobic pocket, and the main difference between the two subtypes lies in the size of this pocket, which is smaller in the case of the MT$_1$ subtype. Moreover, considering the role of the substituent position on the aromatic nucleus, it seems that electronic parameters also contribute to the selectivity and to the antagonist activity.

(**ii) Variations of the Acyl Group on the C-3 Side Chain.** Substitution of the methyl group of **10a** with iodomethyl (**11**), propyl (**12**), vinyl (**14**), or methylamino (**22**) causes a slight decrease in both MT$_1$ and MT$_2$ binding affinities, leading to MT$_1$/MT$_2$ ratios between 15 (**22**) and 78 (**14**). On the other hand, substitution with a furyl substituent (**13**) sharply decreases the MT$_1$ and MT$_2$ affinities but does not affect the MT$_1$/MT$_2$ selectivity ratio (MT$_1$/MT$_2$ = 19). The most interesting results are obtained with the allyl substituent (**18, 19**). The MT$_2$ binding affinity of these two compounds is better than that of melatonin itself, and the best MT$_1$/MT$_2$ selectivity ratio (192) is observed for **19**, which bears a 2-(*m*-methoxybenzyl) substitution and is 8-fold more selective than the lead **10a**. Nevertheless, compound **19** behaves as an MT$_1$ and MT$_2$ partial agonist (Figure 1) whereas its *N*-acetamido analogue **10c** is an antagonist (Figure 1).

These results also show that the *N*-acyl side chain can modulate affinity and selectivity but that its role is

different according to the presence or not of a substitution in the C-2 benzofuran position. The unsaturated allyl substituent seems to be the most favorable for $MT_2$ affinity and selectivity but not for the antagonist potency.

**(iii) Variations of the 5-Methoxy Group.** Deletion of the 5-methoxy group (**10o, 10p**) causes a sharp decrease in the $MT_1$ and $MT_2$ binding affinities, a finding that parallels previous results in other series.[20,33] It seems possible that the $MT_1/MT_2$ ratios of these compounds (15 and 12, respectively) point out a less important role of the methoxy group in the $MT_2$ versus $MT_1$ selectivity. This hypothesis is strengthened by the fact that the same results are obtained by substitution of the methoxy with an ethyl (**10m, 10n**) or a hydroxy (**24**). On the other hand, lengthening the alkyl chain of the ether function to five (**25**) or six (**26**) carbon atoms more strongly decreases the $MT_2$ binding affinity than the $MT_1$ binding affinity and therefore appears unfavorable for $MT_2$ selectivity.

All these results clearly confirm the crucial role played by the 5-methoxy group, in agreement with previous studies.[20,33]

## Conclusions

The results of this study confirm that the benzofuran heterocycle can be considered a good bioisostere of indole in the search for melatonin receptor ligands. Most of the structure−affinity relationships previously described[17] from tissue binding studies are consistent with $MT_1$ and/or $MT_2$ subtypes in, for example, the roles played by the 5-methoxy group, the *N*-acyl substituent, and a 2-phenyl substitution, this last modification leading to a compound, **10q**, which binds more strongly that melatonin itself to both $MT_1$ and $MT_2$ subtypes and behaves as a full agonist.

Introduction of a 2-benzyl group in the C-2 benzofuran position allows access to $MT_2$ selective antagonists, and modulation of the selectivity and of the intrinsic activity can be obtained with suitable modification on the *N*-acyl and the 2-benzyl substituents.

The most selective compounds **10c** and **19** show $MT_1/MT_2$ selectivity ratios of 123 and 192, respectively, and are also very good $MT_2$ ligands with affinities as strong as that of melatonin itself (0.1 nM), but these two compounds differ in their intrinsic activities (antagonist and partial agonist, respectively).

## Experimental Section

**Chemistry.** Melting points were determined on a Buchi SMP-20 capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 297 or a Vector 22 Bruker spectrophotometer. $^1$H NMR spectra were recorded on an 80 SY or an AC 300 Bruker spectrometer. Chemical shifts are reported in $\delta$ units (parts per million) relative to that of $(CH_3)_4Si$. Elemental analyses for new substances were performed by CNRS Laboratories (Vernaison, France). The results obtained are within 0.4% of the theoretical values.

**General Procedure for the Synthesis of 2-Aryl(cyclohexyl)alkylidene-3-oxo-2,3-dihydrobenzo[*b*]furans 5a−5p.** The method adopted for the synthesis of 5-methoxy-3-oxo-2-phenylmethylidene-2,3-dihydrobenzo[*b*]furan (**5a**) is described**.** Benzaldehyde (2.33 g, 0.022 mol) and activated basic aluminum oxide (66 g) were added to a vigorously stirred solution of 3 g (0.018 mol) of **2** in 100 mL of methylene chloride. After 15 min of stirring, aluminum oxide was filtered and washed abundantly with methylene chloride. The filtrate was then concentrated to afford crude **5a**, which was recrystallized from methanol to give 3.4 g (75%) of pure **5a**: mp 133−135 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.95−7.90 (m, 2H), 7.45−7.40 (m, 3H), 7.25−7.20 (m, 3H), 6.90 (s, 1H), 3.85 (s, 3H).

**Data for 5-Methoxy-2-(2-methoxyphenyl)methylidene-3-oxo-2,3-dihydrobenzo[*b*]furan (5b):** recrystallized from methanol; yield 80%; mp 164−166 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.60−7.40 (m, 5H), 7.30 (d, $J$ = 2.7 Hz, 1H), 7.05 (dd, $J$ = 2.7 and 8.3 Hz, 1H), 6.95 (s, 1H), 3.85 (s, 6H).

**Data for 5-Methoxy-2-(3-methoxyphenyl)methylidene-3-oxo-2,3-dihydrobenzo[*b*]furan (5c):** recrystallized from ethanol (95%); yield 76%; mp 121−123 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.50−7.20 (m, 6H), 6.95−6.90 (m, 1H), 6.85 (s, 1H), 3.90 (s, 3H), 3.85 (s, 3H).

**Data for 5-Methoxy-2-(4-methoxyphenyl)methylidene-3-oxo-2,3-dihydrobenzo[*b*]furan (5d):** recrystallized from methanol; yield 84%; mp 173−175 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.95 (d, $J$ = 8.8 Hz, 2H), 7.50 (d, $J$ = 9.1 Hz, 1H), 7.40 (dd, $J$ = 2.6 and 9.1 Hz, 1H), 7.25 (d, $J$ = 2.6 Hz, 1H), 7.05 (d, $J$ = 8.8 Hz, 2H), 6.95 (s, 1H), 3.85 (s, 3H), 3.80 (s, 3H).

**Data for 2-(3-Fluorophenyl)methylidene-5-methoxy-3-oxo-2,3-dihydrobenzo[*b*]furan (5e):** recrystallized from methanol; yield 70%; mp 144−146 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.85−7.80 (m, 2H), 7.60−7.50 (m, 2H), 7.40 (dd, $J$ = 2.8 and 9.1 Hz, 1H), 7.35−7.30 (m, 1H), 7.25 (d, $J$ = 2.8 Hz, 1H), 7.00 (s, 1H), 3.85 (s, 3H).

**Data for 5-Methoxy-3-oxo-2-(3-trifluoromethylphenyl)-methylidene-2,3-dihydrobenzo[*b*]furan (5f):** recrystallized from ethanol; yield 87%; mp 147−149 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.35−8.30 (m, 2H), 7.85−7.75 (m, 2H), 7.55 (d, $J$ = 9.0 Hz, 1H), 7.40 (dd, $J$ = 2.7 and 9.0 Hz, 1H), 7.30 (d, $J$ = 2.7 Hz, 1H), 7.10 (s, 1H), 3.85 (s, 3H).

**Data for 2-(3-Chlorophenyl)methylidene-5-methoxy-3-oxo-2,3-dihydrobenzo[*b*]furan (5g):** recrystallized from ethanol; yield 80%; mp 123−125 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.05−7.95 (m, 2H), 7.55−7.50 (m, 3H), 7.40 (dd, $J$ = 2.5 and 8.9 Hz, 1H), 7.25 (d, $J$ = 2.5 Hz, 1H), 6.95 (s, 1H), 3.85 (s, 3H).

**Data for 2-(2,6-Dichlorophenyl)methylidene-5-methoxy-3-oxo-2,3-dihydrobenzo[*b*]furan (5h):** recrystallized from methanol; yield 91%; mp 163−165 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.65 (d, $J$ = 7.9 Hz, 2H), 7.50 (t, $J$ = 7.9 Hz, 1H), 7.40−7.35 (m, 3H), 6.95 (s, 1H), 3.85 (s, 3H).

**Data for 5-Methoxy-3-oxo-2-(3,5-bistrifluoromethylphenyl)methylidene-2,3-dihydrobenzo[*b*]furan (5i):** recrystallized from ethyl acetate; yield 80%; mp 202−204 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.65 (s, 2H), 8.20 (s, 1H), 7.60 (d, $J$ = 9.0 Hz, 1H), 7.45 (dd, $J$ = 2.7 and 9.0 Hz, 1H), 7.30 (d, $J$ = 2.7 Hz, 1H), 7.20 (s, 1H), 3.85 (s, 3H).

**Data for 2-Cyclohexylmethylidene-5-methoxy-3-oxo-2,3-dihydrobenzo[*b*]furan (5j):** recrystallized from ethanol (95%); yield 82%; mp 68−70 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.45 (d, $J$ = 9.0 Hz, 1H), 7.35 (dd, $J$ = 2.2 and 9.0 Hz, 1H), 7.20 (d, $J$ = 2.2 Hz, 1H), 6.00 (s, 1H), 3.80 (s, 3H), 2.65−2.60 (m, 1H), 1.75−1.25 (m, 10H).

**Data for 5-Methoxy-3-oxo-2-(pyridin-3-yl)methylidene-2,3-dihydrobenzo[*b*]furan (5k):** recrystallized from ethanol (95%); yield 72%; mp 157−159 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.10 (d, $J$ = 1.6 Hz, 1H), 8.60 (dd, $J$ = 1.6 and 8.1 Hz, 1H), 8.40 (d, $J$ = 8.1 Hz, 1H), 7.55 (m, $J$ = 8.1 and 8.9 Hz, 2H), 7.45 (dd, $J$ = 2.8 and 8.9 Hz, 1H), 7.30 (d, $J$ = 2.8 Hz, 1H), 7.00 (s, 1H), 3.85 (s, 3H).

**Data for 5-Methoxy-3-oxo-2-(3-phenylpropen-2-ylidene)-2,3-dihydrobenzo[*b*]furan (5l):** recrystallized from methanol; yield 80%; mp 163−165 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.55−7.15 (m, 9H), 7.05 (d, $J$ = 15.4 Hz, 1H), 6.80−6.75 (m, 1H), 3.85 (s, 3H).

**Data for 5-Ethyl-3-oxo-2-phenylmethylidene-2,3-dihydrobenzo[*b*]furan (5m):** recrystallized from ethanol (95%); yield 75%; mp 70−72 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.70

(dd, $J$ = 1.2 and 8.3 Hz, 2H), 7.65−7.60 (m, 1H), 7.45−7.35 (m, 5H), 6.90 (s, 1H), 2.70 (q, $J$ = 7.5 Hz, 2H), 1.25 (t, $J$ = 7.5 Hz, 3H).

**Data for 5-Ethyl-3-oxo-2-(3-methoxyphenyl)methylidene-2,3-dihydrobenzo[*b*]furan (5n):** recrystallized from ethanol (95%); yield 72%; mp 130−132 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.70−7.40 (m, 6H), 7.05 (dd, $J$ = 2.3 and 8.0 Hz, 1H), 6.90 (s, 1H), 3.85 (s, 3H), 2.70 (q, $J$ = 7.6 Hz, 2H), 1.20 (t, $J$ = 7.6 Hz, 3H).

**Data for 3-Oxo-2-phenylmethylidene-2,3-dihydrobenzo[*b*]furan (5o):** recrystallized from ethanol (95%); yield 75%; mp 112−114 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.95−7.90 (m, 2H), 7.80−7.75 (m, 1H), 7.70−7.65 (m, 1H), 7.50−7.20 (m, 5H), 6.90 (s, 1H).

**Data for 2-(3-Methoxyphenyl)methylidene-3-oxo-2,3-dihydrobenzo[*b*]furan (5p):** recrystallized from ethanol (95%); yield 78%; mp 119−121 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.80−7.75 (m, 1H), 7.65−7.60 (m, 1H), 7.55−7.45 (m, 2H), 7.40−7.30 (m, 2H), 7.20−7.15 (m, 1H), 7.00−6.95 (m, 1H), 6.85 (s, 1H), 3.90 (s, 3H).

**General Procedure for the Synthesis of 3-Oxo-2-aryl-(cyclohexyl)alkyl-2,3-dihydrobenzo[*b*]furans 6a−6p.** The method adopted for the synthesis of 2-benzyl-5-methoxy-3-oxo-2,3-dihydrobenzo[*b*]furan (**6a**) is described. A solution of 1.95 g (0.007 mol) of **5a** in 400 mL of methanol and 100 mL of dioxane was hydrogenated over 10% Pd/C (0.2 g) at atmospheric pressure for 1 h. After filtration and evaporation, the residue was purified by column chromatography ($SiO_2$, ethyl acetate/petroleum ether (2:8)) to give 1.8 g (92%) of pure **6a**: oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.30−7.20 (m, 6H), 7.05−7.00 (m, 2H), 4.80 (dd, $J$ = 3.3 and 8.6 Hz, 1H), 3.80 (s, 3H), 3.35 (dd, $J$ = 3.3 and 14.6 Hz, 1H), 3.00 (dd, $J$ = 8.6 and 14.6 Hz, 1H).

**Data for 5-Methoxy-2-(2-methoxybenzyl)-3-oxo-2,3-dihydrobenzo[*b*]furan (6b):** purified by column chromatography ($SiO_2$, ethyl acetate/petroleum ether (2:8)); yield 92%; mp 100−102 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.30−7.20 (m, 4H), 7.10−6.90 (m, 3H), 4.95 (dd, $J$ = 3.6 and 10.1 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.50 (dd, $J$ = 3.6 and 14.4 Hz, 1H), 2.75 (dd, $J$ = 10.1 and 14.4 Hz, 1H).

**Data for 5-Methoxy-2-(3-methoxybenzyl)-3-oxo-2,3-dihydrobenzo[*b*]furan (6c):** purified by column chromatography ($SiO_2$, ethyl acetate/petroleum ether (2:8)); yield 91%; oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.30−7.20 (m, 2H), 7.10−6.75 (m, 5H), 4.80 (dd, $J$ = 3.4 and 8.8 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.30 (dd, $J$ = 3.4 and 14.7 Hz, 1H), 2.95 (dd, $J$ = 8.8 and 14.7 Hz, 1H).

**Data for 5-Methoxy-2-(4-methoxybenzyl)-3-oxo-2,3-dihydrobenzo[*b*]furan (6d):** purified by column chromatography ($SiO_2$, ethyl acetate/petroleum ether (2:8)); yield 79%; mp 81−83 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.30 (dd, $J$ = 2.7 and 9.1 Hz, 1H), 7.20−7.15 (m, 3H), 7.00 (d, $J$ = 2.7 Hz, 1H), 6.80 (d, $J$ = 8.8 Hz, 2H), 5.00 (dd, $J$ = 4.0 and 7.7 Hz, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.20 (dd, $J$ = 4.0 and 14.7 Hz, 1H), 2.90 (dd, $J$ = 7.7 and 14.7 Hz, 1H).

**Data for 2-(3-Fluorobenzyl)-5-methoxy-3-oxo-2,3-dihydrobenzo[*b*]furan (6e):** purified by column chromatography ($SiO_2$, ethyl acetate/petroleum ether (2:8)); yield 75%; mp 74−76 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.35−7.05 (m, 7H), 5.10 (dd, $J$ = 4.2 and 8.3 Hz, 1H), 3.75 (s, 3H), 3.25 (dd, $J$ = 4.2 and 14.8 Hz, 1H), 2.95 (dd, $J$ = 8.3 and 14.8 Hz, 1H).

**Data for 5-Methoxy-3-oxo-2-(3-trifluoromethylbenzyl)-2,3-dihydrobenzo[*b*]furan (6f):** recrystallized from ethanol; yield 78%; mp 93−95 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.65−7.50 (m, 4H), 7.30 (dd, $J$ = 2.7 and 8.9 Hz, 1H), 7.20 (d, $J$ = 8.9 Hz, 1H), 7.05 (d, $J$ = 2.7 Hz, 1H), 5.20 (dd, $J$ = 4.2 and 8.4 Hz, 1H), 3.75 (s, 3H), 3.35 (dd, $J$ = 4.2 and 14.8 Hz, 1H), 3.10 (dd, $J$ = 8.4 and 14.8 Hz, 1H).

**Data for 2-(3-Chlorobenzyl)-5-methoxy-3-oxo-2,3-dihydrobenzo[*b*]furan (6g):** recrystallized from ethanol; yield 92%; mp 90−92 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.40−7.20 (m, 6H), 7.05 (d, $J$ = 2.5 Hz, 1H), 5.15 (dd, $J$ = 3.8 and 8.5 Hz, 1H), 3.75 (s, 3H), 3.30 (dd, $J$ = 3.8 and 14.6 Hz, 1H), 3.00 (dd, $J$ = 8.5 and 14.6 Hz, 1H).

**Data for 2-(2,6-Dichlorobenzyl)-5-methoxy-3-oxo-2,3-dihydrobenzo[*b*]furan (6h):** recrystallized from ethanol (95%); yield 82%; mp 133−135 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.55 (d, $J$ = 7.9 Hz, 2H), 7.40−7.35 (m, 2H), 7.20 (d, $J$ = 9.0 Hz, 1H), 7.10 (d, $J$ = 3.0 Hz, 1H), 5.00 (dd, $J$ = 4.5 and 10.3 Hz, 1H), 3.80 (s, 3H), 3.35 (dd, $J$ = 4.5 and 14.1 Hz, 1H), 3.25 (dd, $J$ = 10.3 and 14.1 Hz, 1H).

**Data for 5-Methoxy-3-oxo-2-(3,5-bistrifluoromethylbenzyl)-2,3-dihydrobenzo[*b*]furan (6i):** recrystallized from ethanol; yield 90%; mp 120−122 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.05 (s, 2H), 8.00 (s, 1H), 7.35 (dd, $J$ = 2.7 and 9.1 Hz, 1H), 7.20 (d, $J$ = 9.1 Hz, 1H), 7.05 (d, $J$ = 2.7 Hz, 1H), 5.30 (dd, $J$ = 4.3 and 8.8 Hz, 1H), 3.75 (s, 3H), 3.35 (dd, $J$ = 4.3 and 14.8 Hz, 1H), 3.25 (dd, $J$ = 8.8 and 14.8 Hz, 1H).

**Data for 2-Cyclohexylmethyl-5-methoxy-3-oxo-2,3-dihydrobenzo[*b*]furan (6j):** recrystallized from ethanol (95%); yield 80%; mp 65−67 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.35 (dd, $J$ = 2.9 and 8.7 Hz, 1H), 7.20 (d, $J$ = 8.7 Hz, 1H), 7.05 (d, $J$ = 2.9 Hz, 1H), 4.85 (dd, $J$ = 3.2 and 9.9 Hz, 1H), 3.80 (s, 3H), 1.85−0.90 (m, 13H).

**Data for 5-Methoxy-3-oxo-2-(pyridin-3-ylmethyl)-2,3-dihydrobenzo[*b*]furan (6k):** purified by column chromatography ($SiO_2$, acetone/toluene/cyclohexane (5:3:2)); yield 94%; oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.50−8.25 (m, 3H), 7.30−7.05 (m, 4H), 5.15 (dd, $J$ = 4.4 and 7.7 Hz, 1H), 3.75 (s, 3H), 3.30 (dd, $J$ = 4.4 and 14.5 Hz, 1H), 3.05 (dd, $J$ = 7.7 and 14.5 Hz, 1H).

**Data for 5-Methoxy-3-oxo-2-(3-phenylprop-1-yl)-2,3-dihydrobenzo[*b*]furan (6l):** purified by column chromatography ($SiO_2$, ethyl acetate/petroleum ether (2:8)); yield 93%; oil; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.35−7.10 (m, 8H), 4.80 (s, 1H), 3.80 (s, 3H), 2.65−2.55 (m, 4H), 1.70−1.65 (m, 2 H).

**Data for 2-Benzyl-5-ethyl-3-oxo-2,3-dihydrobenzo[*b*]-furan (6m):** purified by column chromatography ($SiO_2$, ethyl acetate/petroleum ether (2:8)); yield 90%; oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.45−7.40 (m, 2H), 7.35−7.25 (m, 5H), 7.00 (d, $J$ = 7.2 Hz, 1H), 4.80 (dd, $J$ = 3.6 and 8.7 Hz, 1H), 3.35 (dd, $J$ = 3.6 and 14.8 Hz, 1H), 2.95 (dd, $J$ = 8.7 and 14.8 Hz, 1H), 2.55 (q, $J$ = 7.6 Hz, 2H), 1.20 (t, $J$ = 7.6 Hz, 3H).

**Data for 5-Ethyl-2-(3-methoxybenzyl)-3-oxo-2,3-dihydrobenzo[*b*]furan (6n):** purified by column chromatography ($SiO_2$, ethyl acetate/petroleum ether (2:8)); yield 80%; oil; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.55−6.80 (m, 7H), 5.10 (dd, $J$ = 3.9 and 8.5 Hz, 1H), 3.75 (s, 3H), 3.20 (dd, $J$ = 3.9 and 14.6 Hz, 1H), 2.90 (dd, $J$ = 8.5 and 14.6 Hz, 1H), 2.30 (q, $J$ = 7.6 Hz, 2H), 1.15 (t, $J$ = 7.6 Hz, 3H).

**Data for 2-Benzyl-3-oxo-2,3-dihydrobenzo[*b*]furan (6o):** purified by column chromatography ($SiO_2$, ethyl acetate/petroleum ether (2:8)); yield 88%; oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.60−7.50 (m, 2H), 7.40−7.00 (m, 7H), 4.75 (dd, $J$ = 3.6 and 8.8 Hz, 1H), 3.40 (dd, $J$ = 3.6 and 14.5 Hz, 1H), 2.90 (dd, $J$ = 8.8 and 14.5 Hz, 1H).

**Data for 2-(3-Methoxybenzyl)-3-oxo-2,3-dihydrobenzo-[*b*]furan (6p):** recrystallized from propan-2-ol; yield 85%; mp 89−91 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.65−7.55 (m, 2H), 7.25−7.20 (m, 1H), 7.10−7.00 (m, 2H), 6.95−6.85 (m, 2H), 6.75 (dd, $J$ = 2.2 and 8.2 Hz, 1H), 4.75 (dd, $J$ = 3.6 and 8.8 Hz, 1H), 3.75 (s, 3H), 3.35 (dd, $J$ = 3.6 and 14.6 Hz, 1H), 2.95 (dd, $J$ = 8.8 and 14.6 Hz, 1H).

**General Procedure for the Synthesis of 2-(2-Aryl-(cyclohexyl)alkylbenzo[*b*]furan-3-yl) Acetonitriles 8a−8p.** The method adopted for the synthesis of 2-(2-benzyl-5-methoxybenzo[*b*]furan-3-yl) acetonitrile (**8a**) is described. Under stirring and $N_2$, a solution of 2.65 g (0.015 mol) of diethyl cyanomethylphosphonate in 10 mL of anhydrous THF was added dropwise to a mixture of 0.6 g (0.015 mol) of NaH (60% in oil) in 30 mL of anhydrous THF cooled to −10 °C. After 30 min in these conditions and addition of 10 mL of HMPT, a solution of 2.54 g (0.010 mol) of **6a** in 50 mL of anhydrous THF was added dropwise, and the mixture was stirred at room temperature for 1 h and 30 min. The mixture was then poured into water and extracted with ether. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude **8a**, which was

purified by column chromatography ($SiO_2$, ethyl acetate/ petroleum ether (2:8)) to give 2.02 g (73%) of pure **8a**: mp 68−70 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.40−7.20 (m, 6H), 7.00−6.85 (m, 2 H), 4.10 (s, 2H), 3.75 (s, 3H), 3.60 (s, 2H).

**Data for 2-[5-Methoxy-2-(2-methoxybenzyl)benzo[*b*]furan-3-yl] Acetonitrile (8b):** purified by column chromatography ($SiO_2$, ethyl acetate/ petroleum ether (2:8)); yield 83%; mp 121−123 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.30−7.25 (m, 4H), 7.00−6.85 (m, 3H), 4.10 (s, 2H), 3.85 (s, 6H), 3.75 (s, 2H).

**Data for 2-[5-Methoxy-2-(3-methoxybenzyl)benzo[*b*]furan-3-yl] Acetonitrile (8c):** recrystallized from toluene/ cyclohexane (3:1); yield 83%; mp 80−82 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.40 (dd, $J$ = 2.0 and 9.1 Hz, 1H), 7.30−7.20 (m, 2H), 6.90−6.80 (m, 4H), 4.20 (s, 4H), 3.80 (s, 3H), 3.75 (s, 3H).

**Data for 2-[5-Methoxy-2-(4-methoxybenzyl)benzo[*b*]furan-3-yl] acetonitrile (8d):** purified by column chromatography ($SiO_2$, ethyl acetate/petroleum ether (3:7)); yield 70%; mp 82−84 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.40 (d, $J$ = 8.7 Hz, 1H), 7.25−6.80 (m, 6H), 4.20 (s, 2H), 4.15 (s, 2H), 3.80 (s, 3H), 3.70 (s, 3H).

**Data for 2-[2-(3-Fluorobenzyl)-5-methoxybenzo[*b*]furan-3-yl] Acetonitrile (8e):** recrystallized from ethanol/ water (1:1); yield 70%; mp 66−68 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.45−7.35 (m, 2H), 7.20−7.05 (m, 4H), 6.90 (m, $J$ = 8.6 Hz, 1H), 4.25 (s, 2H), 4.20 (s, 2H), 3.80 (s, 3H).

**Data for 2-[5-Methoxy-2-(3-trifluoromethylbenzyl)benzo[*b*]furan-3-yl] acetonitrile (8f):** recrystallized from ethyl acetate/petroleum ether (2:8); yield 70%; mp 115−117 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.65−7.55 (m, 4H), 7.40 (d, $J$ = 8.9 Hz, 1H), 7.20 (d, $J$ = 2.7 Hz, 1H), 6.90 (dd, $J$ = 2.7 and 8.9 Hz, 1H), 4.35 (s, 2H), 4.25 (s, 2H), 3.80 (s, 3H).

**Data for 2-[2-(3-Chlorobenzyl)-5-methoxybenzo[*b*]furan-3-yl] Acetonitrile (8g):** recrystallized from cyclohexane; yield 60%; mp 81−83 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.45−7.25 (m, 6H), 6.90 (dd, $J$ = 2.5 and 9.0 Hz, 1H), 4.25 (s, 4H), 3.80 (s, 3H).

**Data for 2-[2-(2,6-Dichlorobenzyl)-5-methoxybenzo[*b*]furan-3-yl] Acetonitrile (8h):** recrystallized from cyclohexane/toluene (1:3); yield 69%; mp 185−187 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.55 (d, $J$ = 8.1 Hz, 2H), 7.40−7.35 (m, 2H), 7.20 (d, $J$ = 2.6 Hz, 1H), 6.85 (dd, $J$ = 2.6 and 8.8 Hz, 1H), 4.50 (s, 2H), 4.20 (s, 2H), 3.80 (s, 3H).

**Data for 2-[5-Methoxy-2-(3,5-bistrifluoromethylbenzyl)benzo[*b*]furan-3-yl] Acetonitrile (8i):** recrystallized from cyclohexane; yield 80%; mp 111−113 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.00 (s, 3H), 7.45 (d, $J$ = 9.0 Hz, 1H), 7.25 (d, $J$ = 2.7 Hz, 1H), 6.90 (dd, $J$ = 2.7 and 9.0 Hz, 1H), 4.50 (s, 2H), 4.25 (s, 2H), 3.80 (s, 3H).

**Data for 2-(2-Cyclohexylmethyl-5-methoxybenzo[*b*]furan-3-yl) Acetonitrile (8j):** recrystallized from cyclohexane; yield 70%; mp 72−74 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.40 (d, $J$ = 9.2 Hz, 1H), 7.15 (d, $J$ = 2.9 Hz, 1H), 6.85 (dd, $J$ = 2.9 and 9.2 Hz, 1H), 4.00 (s, 2H), 3.80 (s, 3H), 2.65 (d, $J$ = 6.8 Hz, 2H), 1.60−0.95 (m, 11H).

**Data for 2-[5-Methoxy-2-(pyridin-3-ylmethyl)benzo[b]furan-3-yl] Acetonitrile (8k):** recrystallized from toluene; yield 63%; mp 122−124 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.55 (d, $J$ = 1.6 Hz, 1H), 8.45 (dd, $J$ = 1.6 and 5.5 Hz, 1H), 7.70 (d, $J$ = 5.5 Hz, 1H), 7.45−7.35 (m, 2H), 7.20 (d, $J$ = 2.7 Hz, 1H), 6.90 (dd, $J$ = 2.7 and 9.1 Hz, 1H), 4.30 (s, 2H), 4.25 (s, 2H), 3.80 (s, 3H).

**Data for 2-[5-Methoxy-2-(3-phenylprop-1-yl)benzo[*b*]furan-3-yl] Acetonitrile (8l):** purified by column chromatography ($SiO_2$, ethyl acetate/petroleum ether (2:8)); yield 75%; oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.35−6.85 (m, 8H), 3.85 (s, 3H), 3.55 (s, 2H), 2.80−2.65 (m, 4H), 2.10−2.05 (m, 2H).

**Data for 2-(2-Benzyl-5-ethylbenzo[*b*]furan-3-yl) Acetonitrile (8m):** purified by column chromatography ($SiO_2$, ethyl acetate/petroleum ether (2:8)); yield 50%; oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.45−6.90 (m, 8H), 4.15 (s, 2H), 3.65 (s, 2H), 2.75 (q, $J$ = 7.5 Hz, 2H), 1.30 (t, $J$ = 7.5 Hz, 3H).

**Data for 2-[5-Ethyl-2-(3-methoxybenzyl)benzo[*b*]furan-3-yl] Acetonitrile (8n):** purified by column chromatography ($SiO_2$, ethyl acetate/petroleum ether (2:8)); yield 68%; oil; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.45−6.80 (m, 7H), 4.20 (s, 4H), 3.70 (s, 3H), 2.70 (q, $J$ = 7.6 Hz, 2H), 1.20 (t, $J$ = 7.6 Hz, 3H).

**Data for 2-(2-Benzylbenzo[*b*]furan-3-yl) Acetonitrile (8o):** purified by column chromatography ($SiO_2$, ethyl acetate/ petroleum ether (2:8)); yield 73%; oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.50−7.45 (m, 1H),7.30−7.25 (m, 1H), 6.90−6.70 (m, 7H), 4.20 (s, 4H).

**Data for 2-[2-(3-Methoxybenzyl)benzo[*b*]furan-3-yl] Acetonitrile (8p):** purified by column chromatography ($SiO_2$, ethyl acetate/petroleum ether (2:8)); yield 73%; oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.50−7.45 (m, 1H), 7.30−7.25 (m, 1H), 7.20−7.10 (m, 3H), 6.80−6.70 (m, 3H), 4.10 (s, 4H), 3.70 (s, 3H).

**2-(5-Methoxy-2-phenylbenzo[*b*]furan-3-yl) Acetonitrile (8q).** Under stirring and $N_2$, 0.085 g (0.0005 mol) of AIBN and 1.87 g (0.0105 mol) of NBS were added to a solution of 2.5 g (0.0105 mol) of **7** in 50 mL of $CCl_4$, and the mixture was refluxed for 2 h and 30 min. After cooling and filtration, the filtrate was concentrated and the residue was dissolved in 5 mL of DMSO and added to a solution of 0.565 g (0.0115 mol) of sodium cyanide in 5 mL of DMSO at 60 °C. After 4 h at this temperature, the mixture was poured into ice water, giving a precipitate which was filtered, purified by column chromatography ($SiO_2$, cyclohexane/ethyl acetate (8:2)), and recrystallized from cyclohexane to give 1.24 g (45%) of pure **8q**: mp 105−107 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.75−7.40 (m, 6H), 7.10 (d, $J$ = 2.7 Hz, 1H), 7.00 (dd, $J$ = 2.7 and 8.9 Hz, 1H), 3.95 (s, 3H), 3.90 (s, 2H).

**General Procedure A for the Synthesis of 2-(Benzo[*b*]furan-3-yl) Ethylamine Hydrochlorides 9a−9d, 9i, 9k, 9l, 9m, and 9o−9q**. The method adopted for the synthesis of 2-(2-benzyl-5-methoxybenzo[*b*]furan-3-yl) ethylamine hydrochloride (**9a**) is described. An $NH_3$-oversaturated solution of 2.77 g (0.010 mol) of **8a** in 100 mL of ethanol was hydrogenated over Raney nickel under pressure (50 bar) at 60 °C for 4 h and 30 min. After filtration and evaporation, the oil was dissolved in dry ether and treated with HCl gas to give, after filtration, 2 g (65%) of **9a**, which was of sufficient purity to be used in subsequent reactions: mp 174−176 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.40 (s, 3H), 7.50−7.10 (m, 7H), 6.80 (dd, $J$ = 2.5 and 8.9 Hz, 1H), 4.20 (s, 2H), 3.80 (s, 3H), 3.20−2.90 (m, 4H).

**Data for 2-[5-Methoxy-2-(2-methoxybenzyl)benzo[*b*]furan-3-yl] Ethylamine Hydrochloride (9b):** yield 74%; mp 181−183 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.20 (s, 3H), 7.35−6.80 (m, 7H), 4.05 (s, 2H), 3.80 (s, 6H), 3.00 (s, 4H).

**Data for 2-[5-Methoxy-2-(3-methoxybenzyl)benzo[*b*]furan-3-yl] Ethylamine Hydrochloride (9c):** yield 67%; mp 135−137 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.20 (s, 3H), 7.45−6.80 (m, 7H), 4.10 (s, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.05−3.00 (m, 4H).

**Data for 2-[5-Methoxy-2-(4-methoxybenzyl)benzo[*b*]furan-3-yl] Ethylamine Hydrochloride (9d):** yield 72%; mp 110−112 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.10 (s, 3H), 7.30−6.70 (m, 7H), 4.00 (s, 2H), 3.75 (s, 3H), 3.65 (s, 3H), 2.95 (s, 4H).

**Data for 2-[5-Methoxy-2-(3,5-bistrifluoromethylbenzyl)benzo[*b*]furan-3-yl] Ethylamine Hydrochloride (9i):** yield 87%; mp 209−211 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.20 (s, 3H), 8.05 (s, 2H), 8.00 (s, 1H), 7.40 (d, $J$ = 8.9 Hz, 1H), 7.30 (d, $J$ = 2.7 Hz, 1H), 6.85 (dd, $J$ = 2.7 and 8.9 Hz, 1H), 4.45 (s, 2H), 3.80 (s, 3H), 3.15−3.05 (m, 4H).

**Data for 2-[5-Methoxy-2-(pyridin-3-ylmethyl)benzo[*b*]furan-3-yl] Ethylamine Dihydrochloride (9k):** yield 67%; mp 217−219 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.95 (s, 1H), 8.80 (s, 1H), 8.40 (s, 1H), 8.20 (s, 3H), 7.95 (s, 1H), 7.35 (d, $J$ = 8.8 Hz, 1H), 7.30 (s, 1H), 6.85 (dd, $J$ = 2.4 and 8.8 Hz, 1H), 4.45 (s, 2H), 3.80 (s, 3H), 3.10 (s, 4H).

**Data for 2-[5-Methoxy-2-(3-phenylprop-1-yl)benzo[*b*]furan-3-yl] Ethylamine Hydrochloride (9l):** yield 56%; mp 121−123 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.10 (s, 3H), 7.40−7.15 (m, 7H), 6.85 (dd, $J$ = 2.2 and 8.9 Hz, 1H), 3.80 (s,

3H), 3.00−2.95 (m, 4H), 2.80 (t, $J$ = 7.5 Hz, 2H), 2.65 (t, $J$ = 7.5 Hz, 2H), 1.95 (m, $J$ = 7.5 Hz, 2H).

**Data for 2-(2-Benzyl-5-ethylbenzo[*b*]furan-3-yl) Ethylamine Hydrochloride (9m):** yield 63%; mp 147−149 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.20 (s, 3H), 7.45−6.80 (m, 8H), 4.10 (s, 2H), 3.05−3.00 (m, 4H), 2.70 (q, $J$ = 7.4 Hz, 2H), 1.20 (t, $J$ = 7.4 Hz, 3H).

**Data for 2-Benzylbenzo[*b*]furan-3-yl Ethylamine Hydrochloride (9o):** yield 65%; mp 193−195 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.25 (s, 3H), 7.70 (s, 1H), 7.45 (s, 1H), 7.30−7.20 (m, 7H), 4.20 (s, 2H), 3.10−3.00 (m, 4H).

**Data for 2-[2-(3-Methoxybenzyl)benzo[*b*]furan-3-yl] Ethylamine Hydrochloride (9p):** yield 72%; mp 153−155 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.20 (s, 3H), 7.65 (s, 1H), 7.50 (s, 1H), 7.30−6.25 (m, 3H), 6.90−6.80 (m, 3H), 4.10 (s, 2H), 3.70 (s, 3H), 3.10−2.90 (m, 4H).

**Data for 2-(5-Methoxy-2-phenylbenzo[*b*]furan-3-yl] Ethylamine Hydrochloride (9q):** yield 77%; mp 255−257 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.40 (s, 3H), 7.90−7.40 (m, 7H), 6.95 (dd, $J$ = 2.3 and 8.8 Hz, 1H), 3.85 (s, 3H), 3.40−3.05 (m, 4H).

**General Procedure B for the Synthesis of 2-(Benzo[*b*]furan-3-yl) Ethylamine Hydrochlorides 9e−9h, 9j, and 9n.** The method adopted for the synthesis of 2-[2-(3-fluorobenzyl)-5-methoxybenzo[*b*]furan-3-yl] ethylamine hydrochloride (**9e**) is described. Under $N_2$, a solution of 2.95 g (0.010 mol) of **8e** in 15 mL of anhydrous THF was added dropwise to 30 mL (0.03 mol) of borane−tetrahydrofuran complex, 1 M solution in THF. After 2 h and 30 min at reflux, 20 mL (0.12 mol) of a 6 N HCl solution was added very slowly and the mixture was refluxed for 30 min. After evaporation, the solid residue was poured into a 12% NaOH solution and the resulting amine was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford an oil which was dissolved in dry ether and treated with HCl gas to give, after filtration, 2 g (65%) of **9e**, which was of sufficient purity to be used in subsequent reactions: mp 171−173 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.25 (s, 3H), 7.40−7.05 (m, 6H), 6.85 (dd, $J$ = 2.6 and 8.8 Hz, 1H), 4.20 (s, 2H), 3.80 (s, 3H), 3.05−3.00 (m, 4H).

**Data for 2-[5-Methoxy-2-(3-trifluoromethylbenzyl)benzo[*b*]furan-3-yl] Ethylamine Hydrochloride (9f):** recrystallized from toluene/cyclohexane (1:1); yield 60%; mp 127−129 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.35 (s, 3H), 7.70−7.60 (m, 4H), 7.40 (d, $J$ = 9.0 Hz, 1H), 7.30 (s, 1H), 6.85 (dd, $J$ = 2.3 and 9.0 Hz, 1H), 4.35 (s, 2H), 3.85 (s, 3H), 3.10−3.05 (m, 4H).

**Data for 2-[2-(3-Chlorobenzyl)-5-methoxybenzo[*b*]furan-3-yl] Ethylamine Hydrochloride (9g):** yield 75%; mp 140−142 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.30 (s, 3H), 7.40−7.30 (m, 6H), 6.80 (dd, $J$ = 2.8 and 8.5 Hz, 1H), 4.20 (s, 2H), 3.80 (s, 3H), 3.05−3.00 (m, 4H).

**Data for 2-[2-(2,6-Dichlorobenzyl)-5-methoxybenzo[*b*]furan-3-yl] Ethylamine Hydrochloride (9h):** yield 55%; mp 244−246 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.05 (s, 3H), 7.55 (d, $J$ = 7.6 Hz, 2H), 7.35 (m, $J$ = 7.6 and 8.9 Hz, 2H), 7.25 (d, $J$ = 2.6 Hz, 1H), 6.80 (dd, $J$ = 2.6 and 8.9 Hz, 1H), 4.45 (s, 2H), 3.80 (s, 3H), 3.10 (s, 4H).

**Data for 2-(2-Cyclohexylmethyl-5-methoxybenzo[*b*]furan-3-yl) Ethylamine Hydrochloride (9j):** recrystallized from cyclohexane; yield 45%; mp 194−196 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.95 (s, 3H), 7.40 (d, $J$ = 8.8 Hz, 1H), 7.15 (d, $J$ = 2.4 Hz, 1H), 6.80 (dd, $J$ = 2.4 and 8.8 Hz, 1H), 3.80 (s, 3H), 3.00−2.90 (m, 4H), 2.65 (d, $J$ = 6.8 Hz, 2H), 1.65−1.00 (m, 11H).

**Data for 2-[5-Ethyl-2-(3-methoxybenzyl)benzo[*b*]furan-3-yl] Ethylamine Hydrochloride (9n):** recrystallized from ethyl acetate; yield 57%; mp 152−154 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.20 (s, 3H), 7.45−6.85 (m, 7H), 4.10 (s, 2H), 3.75 (s, 3H), 3.05 (s, 4H), 2.70 (q, $J$ = 7.4 Hz, 2H), 1.20 (t, $J$ = 7.4 Hz, 3H).

**General Procedure A for the Synthesis of the *N*-Acylated Derivatives 10a−10d, 10i, 10j, 10l, 10m, 10o, and 10p.** The method adopted for the synthesis of *N*-acetyl-2-(2-benzyl-5-methoxybenzo[*b*]furan-3-yl) ethylamine (**10a**) is described. A solution of 2.77 g (0.010 mol) of **8a** in 80 mL of acetic anhydride was hydrogenated over Raney nickel under pressure (50 bar) at 60 °C for 6 h. After filtration and evaporation, the oil was cooled and 10 mL of a 10% NaOH solution was added. After 10 min under stirring, the mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude **10a**, which was recrystallized from toluene to give 2.81 g (87%) of pure **10a**: mp 112−114 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.00 (s, 1H), 7.35−7.20 (m, 6H), 7.15 (d, $J$ = 2.6 Hz, 1H), 6.80 (dd, $J$ = 2.6 and 9.0 Hz, 1H), 4.10 (s, 2H), 3.80 (s, 3H), 3.30 (m, $J$ = 6.7 Hz, 2 H), 2.85 (t, $J$ = 6.7 Hz, 2H), 1.75 (s, 3H). Anal. ($C_{20}H_{21}NO_3$) C, H, N.

**Data for *N*-Acetyl-2-[5-methoxy-2-(2-methoxybenzyl)-benzo[b]furan-3-yl] Ethylamine (10b):** recrystallized from toluene/hexane (1:1); yield 65%; mp 102−104 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.00 (s, 1H), 7.30−6.85 (m, 6H), 6.80 (dd, $J$ = 2.5 and 8.9 Hz, 1H), 4.00 (s, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.30 (m, $J$ = 6.7 Hz, 2 H), 2.80 (t, $J$ = 6.7 Hz, 2H), 1.75 (s, 3H). Anal. ($C_{21}H_{23}NO_4$) C, H, N.

**Data for *N*-Acetyl-2-[5-methoxy-2-(3-methoxybenzyl)-benzo[b]furan-3-yl] Ethylamine (10c):** recrystallized from toluene/hexane (1:1); yield 55%; mp 109−111 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.00 (s, 1H), 7.35−6.80 (m, 7H), 4.05 (s, 2H), 3.80 (s, 3H), 3.70 (s, 3H), 3.25 (m, $J$ = 6.7 Hz, 2 H), 2.80 (t, $J$ = 6.7 Hz, 2H), 1.75 (s, 3H). Anal. ($C_{21}H_{23}NO_4$) C, H, N.

**Data for *N*-Acetyl-2-[5-methoxy-2-(4-methoxybenzyl)-benzo[*b*]furan-3-yl] Ethylamine (10d):** recrystallized from toluene; yield 67%; mp 101−103 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.00 (s, 1H), 7.30 (d, $J$ = 9.0 Hz, 1H), 7.15 (m, $J$ = 8.7 Hz, 3H), 6.85 (m, $J$ = 8.7 and 9.0 Hz, 3H), 4.00 (s, 2H), 3.80 (s, 3H), 3.70 (s, 3H), 3.25 (br q, 2 H), 2.80 (s, 2H), 1.75 (s, 3H). Anal. ($C_{21}H_{23}NO_4$) C, H, N.

**Data for *N*-Acetyl-2-[5-methoxy-2-(3,5-bistrifluoromethylbenzyl)benzo[*b*]furan-3-yl] Ethylamine (10i):** recrystallized from toluene/petroleum ether (1:1); yield 54%; mp 124−126 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.00−7.95 (m, 4H), 7.35 (d, $J$ = 9.1 Hz, 1H), 7.15 (d, $J$ = 2.5 Hz, 1H), 6.80 (dd, $J$ = 2.5 and 9.1 Hz, 1H), 4.35 (s, 2H), 3.80 (s, 3H), 3.30 (m, $J$ = 6.6 Hz, 2 H), 2.85 (t, $J$ = 6.6 Hz, 2H), 1.70 (s, 3H). Anal. ($C_{22}H_{19}F_6NO_3$) C, H, F, N.

**Data for *N*-Acetyl-2-(2-cyclohexylmethyl-5-methoxybenzo[*b*]furan-3-yl] Ethylamine (10j):** purified by column chromatography ($SiO_2$, ethyl acetate/methylene chloride (1:1)); yield 62%; oil; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.95 (s, 1H), 7.35 (d, $J$ = 9.1 Hz, 1H), 7.05 (d, $J$ = 2.4 Hz, 1H), 6.80 (dd, $J$ = 2.4 and 9.1 Hz, 1H), 3.75 (s, 3H), 3.20 (m, $J$ = 6.8 Hz, 2 H), 2.70 (t, $J$ = 6.8 Hz, 2H), 2.55 (d, $J$ = 6.7 Hz, 2H), 1.75 (s, 3H), 1.65−1.00 (m, 11H). Anal. ($C_{20}H_{27}NO_3$) C, H, N.

**Data for *N*-Acetyl-2-[5-methoxy-2-(3-phenylprop-1-yl)-benzo[*b*]furan-3-yl] Ethylamine (10l):** recrystallized from toluene/petroleum ether (1:1); yield 60%; mp 101−103 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.95 (s, 1H), 7.35−7.15 (m, 6H), 7.05 (d, $J$ = 2.2 Hz, 1H), 6.80 (dd, $J$ = 2.2 and 8.6 Hz, 1H), 3.80 (s, 3H), 3.25 (m, $J$ = 6.7 Hz, 2H), 2.65 (m, $J$ = 6.7 and 7.5 Hz, 6H), 1.95 (m, $J$ = 7.5 Hz, 2H), 1.75 (s, 3H). Anal. ($C_{22}H_{25}NO_3$) C, H, N.

**Data for *N*-Acetyl-2-(2-benzyl-5-ethylbenzo[*b*]furan-3-yl) Ethylamine (10m):** recrystallized from toluene; yield 65%; mp 100−102 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.90 (s, 1H), 7.35−7.20 (m, 7H), 7.05 (d, $J$ = 8.7 Hz, 1H), 4.05 (s, 2H), 3.30−3.25 (m, 2H), 2.80 (t, $J$ = 6.9 Hz, 2H), 2.65 (q, $J$ = 7.6 Hz, 2H), 1.75 (s, 3H), 1.95 (t, $J$ = 7.6 Hz, 3H). Anal. ($C_{21}H_{23}NO_2$) C, H, N.

**Data for *N*-Acetyl-2-(2-benzylbenzo[*b*]furan-3-yl) Ethylamine (10o):** recrystallized from toluene/cyclohexane (1:1); yield 55%; mp 98−100 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.50 (d, $J$ = 7.0 Hz, 1H), 7.45−7.40 (m, 1H), 7.35−7.30 (m, 7H), 5.40 (s, 1H), 4.10 (s, 2H), 3.50−3.45 (m, 2 H), 2.90−2.85 (t, $J$ = 6.6 Hz, 2H), 1.70 (s, 3H). Anal. ($C_{19}H_{19}NO_2$) C, H, N.

**Data for *N*-Acetyl-2-[2-(3-methoxybenzyl)benzo[*b*]furan-3-yl] Ethylamine (10p):** recrystallized from cyclohexane; yield 63%; mp 99−101 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$

8.00 (t, $J$ = 5.4 Hz, 1H), 7.60−7.55 (m, 1H), 7.45−7.40 (m, 1H), 7.25−7.20 (m, 3H), 6.85−6.80 (m, 3H), 4.10 (s, 2H), 3.50 (s, 3H), 3.30−3.25 (m, 2 H), 2.90 (t, $J$ = 7.1 Hz, 2H), 1.75 (s, 3H). Anal. ($C_{20}H_{21}NO_3$) C, H, N.

**General Procedure B for the Synthesis of the *N*-Acylated Derivatives 10e−10h, 10k, 10n, 10q, and 11−17**. The method adopted for the synthesis of *N*-acetyl-2-[2-(3-fluorobenzyl)-5-methoxybenzo[*b*]furan-3-yl] ethylamine (**10e**) is described. Potassium carbonate (1.38 g, 0.010 mol) was added to a solution of 1.68 g (0.005 mol) of **9e** in 20 mL of water and 60 mL of methylene chloride. After the mixture was stirred for 20 min at 0 °C, 0.78 g (0.010 mol) of acetyl chloride was added dropwise at the same temperature. The reaction mixture was stirred at room temperature for 2 h. The organic phase was separated, washed with water, a 1 N HCl solution, and water until pH 7 was reached, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was recrystallized from toluene to give 1.2 g (71%) of pure **10e**: mp 136−138 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.00 (s, 1H), 7.40−7.05 (m, 6H), 6.80 (dd, $J$ = 2.5 and 8.9 Hz, 1H), 4.10 (s, 2H), 3.80 (s, 3H), 3.30 (m, $J$ = 6.7 Hz, 2 H), 2.80 (t, $J$ = 6.7 Hz, 2H), 1.75 (s, 3H). Anal. ($C_{20}H_{20}FNO_3$) C, H, F, N.

**Data for *N*-Acetyl-2-[5-methoxy-2-(3-trifluoromethylbenzyl)benzo[*b*]furan-3-yl] Ethylamine (10f):** recrystallized from toluene; yield 71%; mp 123−125 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.00 (s, 1H), 7.65−7.55 (m, 4H), 7.35 (d, $J$ = 9.0 Hz, 1H), 7.15 (d, $J$ = 2.6 Hz, 1H), 6.80 (dd, $J$ = 2.6 and 9.0 Hz, 1H), 4.20 (s, 2H), 3.80 (s, 3H), 3.30 (m, $J$ = 6.5 Hz, 2 H), 2.85 (t, $J$ = 6.5 Hz, 2H), 1.75 (s, 3H). Anal. ($C_{21}H_{20}F_3NO_3$) C, H, F, N.

**Data for *N*-Acetyl-2-[2-(3-chlorobenzyl)-5-methoxybenzo[*b*]furan-3-yl] Ethylamine (10g):** recrystallized from toluene/cyclohexane (3:1); yield 51%; mp 114−116 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.00 (s, 1H), 7.65−7.55 (m, 4H), 7.35 (d, $J$ = 9.0 Hz, 1H), 7.15 (d, $J$ = 2.6 Hz, 1H), 6.80 (dd, $J$ = 2.6 and 9.0 Hz, 1H), 4.20 (s, 2H), 3.80 (s, 3H), 3.30 (m, $J$ = 6.5 Hz, 2 H), 2.85 (t, $J$ = 6.5 Hz, 2H), 1.75 (s, 3H). Anal. ($C_{20}H_{20}ClNO_3$) C, H, Cl, N.

**Data for *N*-Acetyl-2-[2-(2,6-dichlorobenzyl)-5-methoxybenzo[*b*]furan-3-yl] Ethylamine (10h):** recrystallized from ethanol/water (1:1); yield 64%; mp 165−167 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.05 (s, 1H), 7.50 (d, $J$ = 8.2 Hz, 2H), 7.35 (m, $J$ = 8.2 and 8.9 Hz, 2H), 7.15 (d, $J$ = 2.6 Hz, 1H), 6.80 (dd, $J$ = 2.6 and 8.9 Hz, 1H), 4.35 (s, 2H), 3.80 (s, 3H), 3.30 (m, $J$ = 6.7 Hz, 2 H), 2.85 (t, $J$ = 6.7 Hz, 2H), 1.80 (s, 3H). Anal. ($C_{20}H_{19}Cl_2NO_3$) C, H, Cl, N.

**Data for *N*-Acetyl-2-[5-methoxy-2-(pyridin-3-ylmethyl)benzo[*b*]furan-3-yl] Ethylamine (10k):** recrystallized from toluene/cyclohexane (1:1); yield 45%; mp 116−118 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.50 (s, 1H), 8.45 (d, $J$ = 5.7 Hz, 1H), 8.00 (s, 1H), 7.65 (d, $J$ = 5.7 Hz, 1H), 7.35−7.30 (m, 2H), 7.10 (d, $J$ = 2.3 Hz, 1H), 6.80 (dd, $J$ = 2.3 and 8.7 Hz, 1H), 4.10 (s, 2H), 3.75 (s, 3H), 3.25 (m, $J$ = 6.7 Hz, 2 H), 2.85 (t, $J$ = 6.7 Hz, 2H), 1.70 (s, 3H). Anal. ($C_{19}H_{20}N_2O_3$) C, H, N.

**Data for *N*-Acetyl-2-[5-ethyl-2-(3-methoxybenzyl)benzo[*b*]furan-3-yl] Ethylamine (10n):** recrystallized from toluene/cyclohexane (9:1); yield 66%; mp 101−103 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.00 (s, 1H), 7.40−6.80 (m, 7H), 4.05 (s, 2H), 3.70 (s, 3H), 3.25 (m, $J$ = 6.8 Hz, 2 H), 2.80 (t, $J$ = 6.8 Hz, 2H), 2.70 (q, $J$ = 7.6 Hz, 2H), 1.75 (s, 3H), 1.20 (t, $J$ = 7.6 Hz, 3H). Anal. ($C_{22}H_{25}NO_3$) C, H, N.

**Data for *N*-Acetyl-2-(5-methoxy-2-phenylbenzo[*b*]furan-3-yl) Ethylamine (10q):** recrystallized from toluene/cyclohexane (1:1); yield 68%; mp 114−116 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.00 (s, 1H), 7.90−7.40 (m, 6H), 7.20 (d, $J$ = 2.2 Hz, 1H), 6.95 (dd, $J$ = 2.2 and 8.8 Hz, 1H), 3.80 (s, 3H), 3.45−3.30 (m, 2 H), 3.00 (t, $J$ = 7.2 Hz, 2H), 1.75 (s, 3H). Anal. ($C_{19}H_{19}NO_3$) C, H, N.

**Data for *N*-Iodoacetyl-2-(2-benzyl-5-methoxybenzo[*b*]furan-3-yl) Ethylamine (11):** recrystallized from toluene; yield 83%; mp 110−112 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.95 (s, 1H), 7.35−7.20 (m, 6H), 7.10 (d, $J$ = 2.5 Hz, 1H), 6.80 (dd, $J$ = 2.5 and 8.8 Hz, 1H), 4.10 (s, 2H), 3.75 (s, 3H), 3.55 (s, 2H), 3.30 (t, $J$ = 7.0 Hz, 2H), 2.80 (t, $J$ = 7.0 Hz, 2H). Anal. ($C_{20}H_{20}NIO_3$) C, H, N.

**Data for *N*-Butanoyl-2-(2-benzyl-5-methoxybenzo[*b*]-furan-3-yl) Ethylamine (12):** recrystallized from hexane; yield 40%; mp 85−87 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.95 (t, $J$ = 5.4 Hz, 1H), 7.40−7.20 (m, 6H), 7.15 (d, $J$ = 2.4 Hz, 1H), 6.80 (dd, $J$ = 2.4 and 8.6 Hz, 1H), 4.05 (s, 2H), 3.75 (s, 3H), 3.30 (dt, $J$ = 5.4 and 6.8 Hz, 2H), 2.80 (t, $J$ = 6.8 Hz, 2H), 2.05 (t, $J$ = 7.2 Hz, 2H), 1.50−1.45 (m, 2H), 0,80 (t, $J$ = 7.2 Hz, 3H). Anal. ($C_{22}H_{25}NO_3$) C, H, N.

**Data for *N*-Furoyl-2-(2-benzyl-5-methoxybenzo[*b*]furan-3-yl) Ethylamine (13):** recrystallized from toluene/cyclohexane; yield 68%; mp 120−122 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.55 (s, 1H), 7.85 (s, 1H), 7.75−7.20 (m, 6H), 7.15 (d, $J$ = 2.2 Hz, 1H), 7.05 (d, $J$ = 3.3 Hz, 1H), 6.80 (dd, $J$ = 2.2 and 8.8 Hz, 1H), 6.60 (q, $J$ = 3.3 Hz, 1H), 4.10 (s, 2H), 3.75 (s, 3H), 3.50 (q, $J$ = 6.7 Hz, 2H), 2.95 (t, $J$ = 6.7 Hz, 2H). Anal. ($C_{23}H_{21}NO_4$) C, H, N.

**Data for *N*-Propen-2-oyl-2-(2-benzyl-5-methoxybenzo-[*b*]furan-3-yl) Ethylamine (14):** purified by column chromatography ($SiO_2$, ethyl acetate/methylene chloride (1:1)); yield 54%; mp 107−109 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.30 (t, $J$ = 5.8 Hz, 1H), 7.40−7.20 (m, 6H), 7.10 (d, $J$ = 2.4 Hz, 1H), 6.80 (dd, $J$ = 2.4 and 8.9 Hz, 1H), 6.20 (dd, $J$ = 9.7 and 17.1 Hz, 1H), 6.10 (dd, $J$ = 2.5 and 17.1 Hz, 1H), 5.55 (dd, $J$ = 2.5 and 9.7 Hz, 1H), 4.05 (s, 2H), 3.80 (s, 3H), 3.30 (dt, $J$ = 5.8 and 6.9 Hz, 2H), 2.85 (t, $J$ = 6.9 Hz, 2H). Anal. ($C_{21}H_{21}NO_3$) C, H, N.

**Data for *N*-Propen-2-oyl-2-[5-methoxy-2-(3-methoxybenzyl)benzo[*b*]furan-3-yl] Ethylamine (15):** recrystallized from toluene; yield 73%; mp 113−115 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.30 (t, $J$ = 5.6 Hz, 1H), 7.35−6.80 (m, 7H), 6.20 (dd, $J$ = 9.5 and 17.0 Hz, 1H), 6.10 (dd, $J$ = 2.7 and 17.0 Hz, 1H), 5.60 (dd, $J$ = 2.7 and 9.5 Hz, 1H), 4.05 (s, 2H), 3.80 (s, 3H), 3.70 (s, 3H), 3.40 (m, $J$ = 6.8 Hz, 2 H), 2.90 (t, $J$ = 6.8 Hz, 2H). Anal. ($C_{22}H_{23}NO_4$) C, H, N.

**Data for *N*-Propen-2-oyl-2-(5-methoxy-2-phenylbenzo-[*b*]furan-3-yl) Ethylamine (16):** recrystallized from cyclohexane; yield 86%; mp 116−118 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.40 (t, $J$ = 5.8 Hz, 1H), 7.85−7.40 (m, 6H), 7.20 (d, $J$ = 2.6 Hz, 1H), 6.90 (dd, $J$ = 2.6 and 9.0 Hz, 1H), 6.20 (dd, $J$ = 9.2 and 17.1 Hz, 1H), 6.10 (dd, $J$ = 3.3 and 17.1 Hz, 1H), 5.60 (dd, $J$ = 3.3 and 9.2 Hz, 1H), 3.80 (s, 3H), 3.50 (m, $J$ = 7.0 Hz, 2 H), 3.05 (t, $J$ = 7.0 Hz, 2H). Anal. ($C_{20}H_{19}NO_3$) C, H, N.

**Data for *N*-Furoyl-2-(5-methoxy-2-phenylbenzo[*b*]furan-3-yl) Ethylamine (17):** recrystallized from ethanol (95%); yield 58%; mp 122−124 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.65 (t, $J$ = 5.9 Hz, 1H), 7.85−7.80 (m, 3H), 7.55−7.40 (m, 4H), 7.25 (d, $J$ = 2.6 Hz, 1H), 7.05 (d, $J$ = 3.6 Hz, 1H), 6.90 (dd, $J$ = 2.6 and 8.7 Hz, 1H), 6.60 (q, $J$ = 3.6 Hz, 1H), 3.80 (s, 3H), 3.55 (q, $J$ = 7.0 Hz, 2 H), 3.10 (t, $J$ = 7.0 Hz, 2H). Anal. ($C_{22}H_{19}NO_4$) C, H, N.

**General Procedure for the Synthesis of the *N*-But-1-en-3-oyl-2-(5-methoxybenzo[*b*]furan-3-yl) Ethylamines 18−20.** The method adopted for the synthesis of *N*-but-1-en-3-oyl-2-(2-benzyl-5-methoxybenzo[*b*]furan-3-yl) ethylamine (**18**) is described. The amine hydrochloride **9a** (0.5 g, 0.0016 mol) was dissolved in 50 mL of water with 0.67 g (0.0048 mol) of $K_2CO_3$, and after 2 h under stirring, the mixture was extracted with ether. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting amine was dissolved in 20 mL of methylene chloride at −20 °C. At this temperature, 0.2 g (0.0023 mol) of vinylacetic acid and 0.45 g (0.0023 mol) of EDCI were dissolved in 30 mL of methylene chloride. After 30 min, the solution of the amine was added dropwise to the mixture of the acid and EDCI. The reaction mixture was stirred at −20 °C for 2 h and at room temperature for 24 h; then, it was washed with a 6 N HCl solution, water, a 10% NaOH solution, and water until pH 7 was reached. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography ($SiO_2$, ethyl acetate/methylene chloride (1:1)), and recrystallized from ethanol/

water (1:3) to give 0.2 g (36%) of pure **18**: mp 90−92 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.00 (s, 1H), 7.35−7.20 (m, 6H), 7.10 (d, $J$ = 2.5 Hz, 1H), 6.70 (dd, $J$ = 2.5 and 8.9 Hz, 1H), 5.90−5.75 (m, 1H), 5.10−5.00 (m, 2H), 4.10 (s, 2H), 3.80 (s, 3H), 3.30−3.25 (m, 2H), 2.90−2.80 (m, 4H). Anal. ($C_{22}H_{23}NO_3$) C, H, N.

**Data for *N*-But-1-en-3-oyl-2-[5-methoxy-2-(3-methoxybenzyl)benzo[*b*]furan-3-yl] Ethylamine (19):** recrystallized from cyclohexane; yield 46%; mp 98−100 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.10 (s, 1H), 7.35−7.20 (m, 2H), 7.10 (d, $J$ = 1.9 Hz, 1H), 6.90−6.70 (m, 4H), 5.90−5.85 (m, 1H), 5.10−5.00 (m, 2H), 4.10 (s, 2H), 3.80 (s, 3H), 3.70 (s, 3H), 3.30−3.25 (m, 2 H), 2.90−2.80 (m, 4H). Anal. ($C_{23}H_{25}NO_4$) C, H, N.

**Data for *N*-But-1-en-3-oyl-2-(5-methoxy-2-phenylbenzo[*b*]furan-3-yl) Ethylamine (20):** recrystallized from cyclohexane; yield 53%; mp 99−101 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.10 (s, 1H), 7.85−7.40 (m, 6H), 7.20 (d, $J$ = 2.3 Hz, 1H), 6.95 (dd, $J$ = 2.3 and 9.1 Hz, 1H), 5.90−5.75 (m, 1H), 5.10−5.00 (m, 2H), 3.80 (s, 3H), 3.40−3.35 (m, 2 H), 3.05 (t, $J$ = 7.0 Hz, 2H), 2.85 (d, $J$ = 6.9 Hz, 2H). Anal. ($C_{21}H_{21}NO_3$) C, H, N.

***N*-But-2-en-3-oyl-2-(5-methoxy-2-phenylbenzo[*b*]furan-3-yl) ethylamine (21).** A solution of vinylacetic acid (0.36 g, 0.0042 mol) in 10 mL of methylene chloride was stirred at −10 °C for 20 min. Then, triethylamine (0.32 g, 0.0032 mol), HOBt (0.43 g, 0.0032 mol), and EDCI (0.61 g, 0.0032 mol) were added, and the mixture was stirred at −10 °C for 30 min. A solution of 0.64 g (0.0021 mol) of **9q** in 10 mL of methylene chloride was cooled at −10 °C and added dropwise. After 18 h of stirring at room temperature, the reaction mixture was washed with water, a 1 N HCl solution, water, a 10% NaOH solution, and water until pH 7 was reached. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was precipitated in petroleum ether and recrystallized from ethanol/water (1:1) to give 0.4 g (57%) of pure **21**: mp 118−120 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.20 (t, 1H), 7.85−7.45 (m, 6H), 7.20 (s, 1H), 6.95 (d, $J$ = 8.8 Hz, 1H), 6.65−6.60 (m, 1H), 5.85 (d, $J$ = 15.3 Hz, 1H), 3.80 (s, 3H), 3.50−3.45 (m, 2 H), 3.05 (t, $J$ = 6.7 Hz, 2H), 1.80 (d, $J$ = 6.5 Hz, 3H). Anal. ($C_{21}H_{21}NO_3$) C, H, N.

**General Procedure for the Synthesis of the Ureas 22 and 23.** The method adopted for the synthesis of *N*-[2-(2-benzyl-5-methoxybenzo[*b*]furan-3-yl)ethyl]-*N*′-methylurea (**22**) is described. A 0.15 g (0.0028 mol) portion of methyl isocyanate was added dropwise to a solution of the amine hydrochloride **9a** (0.754 g, 0.0024 mol) in 10 mL of pyridine. After being stirred for 1 h and 30 min at room temperature, the mixture was poured into ice−water and extracted with ethyl acetate. The organic phase was washed with a 3 N HCl solution and then with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was recrystallized from ethanol/water (1:3) to give 0.24 g (31%) of pure **22**: mp 133−135 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.50−7.20 (m, 6H), 7.10 (d, $J$ = 2.4 Hz, 1H), 6.80 (dd, $J$ = 2.4 and 8.9 Hz, 1H), 5.95 (t, $J$ = 5.8 Hz, 1H), 5.75 (q, $J$ = 4.7 Hz, 1H), 4.10 (s, 2H), 3.80 (s, 3H), 3.25 (td, $J$ = 5.8 and 6.9 Hz, 2 H), 2.80 (t, $J$ = 6.9 Hz, 2H), 2.55 (d, $J$ = 4.7 Hz, 3H). Anal. ($C_{20}H_{22}N_2O_3$) C, H, N.

**Data for *N*-[2-(5-Methoxy-2-phenylbenzo[*b*]furan-3-yl) ethyl]-*N*′-methylurea (23):** recrystallized from toluene; yield 56%; mp 153−155 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.95−7.35 (m, 6H), 7.25 (d, $J$ = 2.7 Hz, 1H), 6.90 (dd, $J$ = 2.7 and 8.9 Hz, 1H), 6.10 (t, $J$ = 5.5 Hz, 1H), 5.80 (q, $J$ = 4.6 Hz, 1H), 3.85 (s, 3H), 3.40−3.25 (m, 2H), 3.00 (t, $J$ = 7.2 Hz, 2H), 2.55 (d, $J$ = 4.6 Hz, 3H). Anal. ($C_{19}H_{20}N_2O_3$) C, H, N.

***N*-Acetyl-2-(2-benzyl-5-hydroxybenzo[*b*]furan-3-yl) Ethylamine (24).** Under $N_2$, a solution of 1.9 g (0.006 mol) of the complex $BBr_3$/$Me_2S$ in 100 mL of methylene chloride was stirred at room temperature for 15 min. A solution of 1 g (0.003 mol) of **10a** in 50 mL of methylene chloride was added dropwise, and the mixture was refluxed for 18 h. After cooling, the mixture was carefully hydrolyzed and concentrated under reduced pressure. The residue was taken off with ethyl acetate, washed with a 1 N $NaHCO_3$ solution, and then extracted with a 20% NaOH solution. The aqueous phases were combined, acidified with a 1 N HCl solution, and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude **24**, which was recrystallized from toluene to give 0.6 g (63%) of pure **24**: mp 160−162 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.10 (s, 1H), 8.00 (t, $J$ = 5.3 Hz, 1H), 7.40−7.15 (m, 6H), 6.90 (d, $J$ = 1.7 Hz, 1H), 6.65 (dd, $J$ = 1.7 and 8.7 Hz, 1H), 4.10 (s, 2H), 3.30 (q, $J$ = 6.7 Hz, 2H), 2.80 (t, $J$ = 6.7 Hz, 2H), 1.80 (s, 3H). Anal. ($C_{19}H_{19}NO_3$) C, H, N.

**General Procedure for the Synthesis of the Ethers 25 and 26.** The method adopted for the synthesis of *N*-acetyl-2-(2-benzyl-5-pentoxybenzo[*b*]furan-3-yl) ethylamine (**25**) is described. A 2.6 mL (0.02 mol) portion of iodopentane was added to a solution of 3.09 g (0.01 mol) of **24** in 100 mL of acetonitrile in the presence of 2.76 g (0.02 mol) of $K_2CO_3$, and the mixture was refluxed for 18 h. After cooling and filtration, the filtrate was concentrated and the residue was dissolved in ethyl acetate and washed with a 10% NaOH solution and then with brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude **25**, which was recrystallized from toluene/petroleum ether (1:1) to give 2.6 g (68%) of pure **25**: mp 71−73 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.00 (s, 1H), 7.35−7.20 (m, 6H), 7.10 (d, $J$ = 2.6 Hz, 1H), 6.80 (dd, $J$ = 2.6 and 8.8 Hz, 1H), 4.05 (s, 2H), 3.95 (t, $J$ = 7.0 Hz, 2H), 3.25 (q, $J$ = 6.8 Hz, 2H), 2.80 (t, $J$ = 6.8 Hz, 2H), 1.75−1.70 (m, 5H), 1.45−1.30 (m, 4H), 0.90 (t, $J$ = 7.0 Hz, 3H). Anal. ($C_{24}H_{29}NO_3$) C, H, N.

**Data for *N*-Acetyl-2-(2-benzyl-5-hexyloxybenzo[*b*]furan-3-yl) ethylamine (26):** recrystallized from ethanol/water (1:1); yield 60%; mp 64−66 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.00 (s, 1H), 7.35−7.20 (m, 6H), 7.10 (d, $J$ = 2.4 Hz, 1H), 6.80 (dd, $J$ = 2.4 and 9.0 Hz, 1H), 4.05 (s, 2H), 3.95 (t, $J$ = 6.9 Hz, 2H), 3.25 (q, $J$ = 6.8 Hz, 2H), 2.80 (t, $J$ = 6.8 Hz, 2H), 1.75−1.70 (m, 5H), 1.50−1.25 (m, 6H), 0.90 (t, $J$ = 6.9 Hz, 3H). Anal. ($C_{25}H_{31}NO_3$) C, H, N.

**Pharmacology. 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).

**Cell Culture.** HEK (provided by A.D. Strosberg, Paris, France) and CHO cell lines stably expressing the human melatonin $MT_1$ or $MT_2$ receptor were grown in DMEM medium supplemented with 10% fetal calf serum, 2 mM glutamine, 100 IU/mL penicillin, and 100 $\mu$g/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 (95000*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.

**Binding Assays.** 2-[$^{125}$I]Iodomelatonin binding assay conditions were essentially as previously described.[35] Briefly, binding was initiated by addition of membrane preparations from stable transfected HEK cells (40 $\mu$g/mL) diluted in binding buffer (50 mM TRIS−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) and the tested drug. Nonspecific binding was defined in the presence of 1 $\mu$M 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. The filters were washed three times with 1 mL of ice-cold 50 mM TRIS−HCl buffer, pH 7.4.

[$^{35}$S]GTP$\gamma$S binding assay was performed according to published methodology.[36] Briefly, membranes from CHO transfected cells and peptides were diluted in binding buffer (20 mM HEPES, pH 7.4, 100 mM NaCl, 3 $\mu$M GDP, 3 mM $MgCl_2$, and 20 $\mu$g/mL saponin). Incubation was started by the addition of 0.2 nM [$^{35}$S]GTP$\gamma$S to the membranes (20 $\mu$g/mL) and drugs,

and further followed for 1 h at room temperature. For experiments with antagonists, the membranes were preincubated with both the melatonin and the antagonist for 30 min prior to the addition of [$^{35}$S]GTP$\gamma$S. Nonspecific binding was defined using cold GTP$\gamma$S (10 $\mu$M). Reaction was stopped by rapid filtration through GF/B filters followed by three successive washes with ice-cold buffer.

The usual levels of [$^{35}$S]GTP$\gamma$S 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 $\mu$M), and 160 and 180 in the presence of GTP$\gamma$S 10 $\mu$M, which defined the nonspecific binding.

Data were analyzed by using the program PRISM (Graph Pad Software Inc., San Diego, CA) to yield $EC_{50}$ (effective concentration 50%) and $E_{max}$ (maximal effect) for agonists. Antagonist potencies are expressed as $pK_B = -(\log K_B)$, with $K_B = IC_{50}/(1 + [Ago]/EC_{50}(ago))$, where $IC_{50}$ is the inhibitory concentration of antagonist that gives 50% inhibition of [$^{35}$S]-GTP$\gamma$S 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.

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