Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry 16 (2008) 4954–4962
Bioorganic & Medicinal Chemistry

Design and synthesis of benzofuranic derivatives as new ligands at the melatonin-binding site MT_3

Mohamed Ettaoussi,[a] Basile Péres,[a] Fréderique Klupsch,[a] Philippe Delagrange,[c] Jean-A. Boutin,[b] Pierre Renard,[c] Daniel-H. Caignard,[c] Philippe Chavatte,[a] Pascal Berthelot,[a] Daniel Lesieur[a] and Saïd Yous[a,*]

[a]*Laboratoire de Chimie Thérapeutique (EA 1043), Faculté des Sciences Pharmaceutiques et Biologiques, Université de Lille, 3, rue du professeur Laguesse, 2, BP 83, 59006 Lille Cedex, France*
[b]*Division de Pharmacologie Moléculaire et Cellulaire, Institut de Recherches Servier, 125 Chemin de Ronde, 78290 Croissy-sur-Seine, France*
[c]*Institut de Recherches Servier, 11 rue des Moulineaux, 92150 Suresnes, France*

Received 10 January 2008; revised 4 March 2008; accepted 14 March 2008
Available online 17 March 2008

Abstract—Benzofuranic analogues of MCA-NAT (5-methoxycarbonylamino-*N*-acetyltryptamine) have been synthesized and evaluated as melatonin receptor ligands. Introduction of a methoxycarbonylamino substituent in the C-5 position of the benzofurane nucleus obtains MT_3 selective ligands. This selectivity can be modulated with suitable variations of the C-5 position and the acyl group on the C-3 side chain.

1. Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine, MLT) (Chart 1) is synthesized and released by the pineal gland in a circadian fashion, with high levels occurring during the night. Indeed its synthesis is regulated by the day–night alternation and by the way MLT transmits to the organism information about the photoperiod.[1]

Melatonin appears to play an important role in the regulation of mammalian circadian rhythms and reproduction functions and has been implicated in a number of pathological states suggesting its therapeutic application in several disorders.[2–5]

To date, two mammalian MLT receptors have been cloned (MT_1 and MT_2).[6,7] Both are G-protein coupled receptors.[8] Another melatonin-binding site with low affinity, referred to as MT_3, was recently identified as the quinone reductase 2 (QR2 EC 1.6.99.2)[9] an enzyme closely related to quinone reductase 1.

Recent works suggest that the MT_3 melatonin-binding site is involved in acute inflammatory responses in the rat[10] and in the regulation of intraocular pressure in the rabbit.[11] The physiological importance of the MT_3/QR2 site is still unknown and therefore is of particular interest to design and synthesize new selective ligands which will provide pharmacological tools to assess and better characterize the role of this melatonin-binding site.[12,13]

An accurate characterization of this binding site mediating specific functions in native tissues can only be made using specific ligands. Unfortunately, only a few MT_3 selective ligands have been reported to date (Chart 1). Among them, prazosin,[14] familiarly known as an α1-adrenoceptor antagonist, acts as an MT_3 selective ligand (IC_{50} = 7.8 nM), 5-methoxycarbonylamino-*N*-acetyltryptamine (MCA-NAT),[15] has been described as a selective MT_3 ligand (IC_{50} = 2.7 nM), nitroindole derivative (S27533)[16] ($K_i \approx 0.3$ nM), and recently, DMHMIO (2,3-dimethoxy 7-hydroxy 10-methyl 5*H* 10*H* indeno(1,2-b)indol-10-one) (K_i = 0.19 nM).[17]

Keywords: Melatonin; MCA-NAT; MT_3 binding site; Benzofuranic ligands; Binding; Quinone reductase 2.
* Corresponding author. Tel./fax: +33 3 20964375; e-mail: said.yous@univ-lille2.fr

0968-0896/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2008.03.036

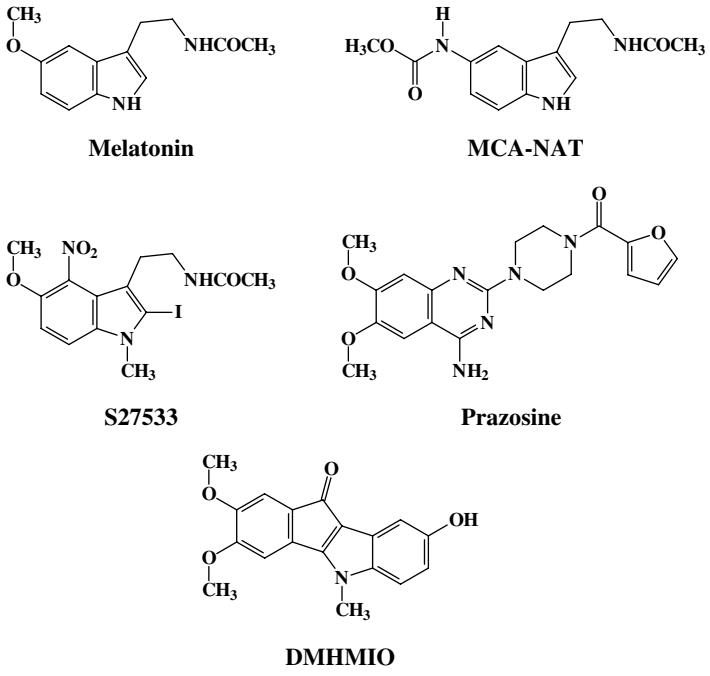


Chart 1. Chemical structures of melatonin and MT_3 ligands.

The known MT_3 ligand MCA-NAT includes a methoxycarbonylamino group in the 5-position. It appeared to us therefore desirable to synthesize its benzofuranic bioisostere (**10a**) as it has been reported that the benzofurane analogues of melatonin are not only metabolically more stable but also very potent for the melatonin receptors.[18,19] Furthermore, in the hope of better modulating the fit to the MT_3 binding site, we replaced the methoxycarbonylamino group of **10a** with ester function (**6a**) and amide groups (**7a**, **8a**, **11**).

In order to explore the role of the *N*-acyl side chain on the binding affinity and the selectivity, we replace the methyl of the acetamido function with, isopropyl, cyclopropyl, cyclopentyl, furyl, and allyl (Table 1).

For all these compounds, the synthesis, the binding data for the human MT_1 and MT_2 receptors and MT_3 binding site are reported.

2. Results and discussion

2.1. Chemistry

The synthetic pathway for compounds 6a-e is outlined in Scheme 1.

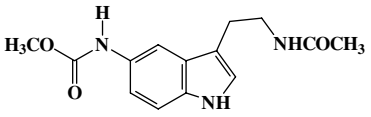
Commercially available 4-acetoxybenzoic acid was converted to acid **1** by treatment with aluminium trichloride in nitrobenzene.[20] First attempts to form bromoacetyl compound **2** using bromine in dichloromethane afforded its dibromated analogue as the major product. Replacing dichloromethane by acetic acid furnished the desired monobrominated compound **2**, which reacted with thionyl chloride and methanol to give ester **3**. Cyclization into benzofuranone was achieved by treatment with potassium carbonate in acetone, and then nitrile **4** was obtained employing Horner-Emmons olefination with diethyl cyanomethylphosphonate.[21] Hydrogenation of nitrile **4** in the presence of platinum oxide in chloroform and methanol led to amine **5**. The *N*-acyl derivatives **6a–e** were prepared from **5** by treatment with the appropriate acid chlorides in the presence of $N(Et)_3$ as base.

Compounds **7(a, c, e)** and **8(a, c, d)** were synthesized from the corresponding esters **6(a, c–e)** according to Scheme 2. Introduction of the carboxamido group was achieved using aqueous ammonia (method A) or formamide and sodium methanolate (method B), whereas treatment with methylamine afforded secondary amide **8(a, c, d)**.

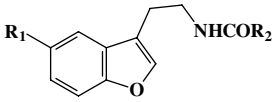
The synthetic sequences used for the transformation of esters **6a–e** into targeted compounds **10a–e** and **11** were as follows (Scheme 3): (1) saponification of the ester group, producing the corresponding acid derivatives **9(a–e)**, (2) preparation of the azide intermediates by reaction with ethyl chloroformate then with sodium azide, and (3) treatment with methanol or trifluoroacetic acid, resulting in carbamates **10(a–e)** and amide **11**, respectively.

Synthesis of the vinylacetamide **10f** was carried out as illustrated in Scheme 4. Ester **4** was saponified to give acid **12**, which was converted into carbamate **13** as previously described. Hydrogenation of the cyano group over Raney nickel in methanol provided amine **14**. A peptide coupling reaction type in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) between the amine **14** and vinylacetic acid gave the amide **10f**.

Table 1. MT_1, MT_2, and MT_3 receptor-binding affinities of benzofuranic compounds



MCANAT



Compound	R_1	R_2	IC_{50} (nM) MT_3	IC_{50} (nM) MT_1	IC_{50} (nM) MT_2	MT_1/ MT_3 MT_2/MT_3
Melatonin	—	—	64.6 ± 0.9	0.2 ± 0.03	0.53 ± 0.06	1/323 1/122
MCA-NAT	—	—	58 ± 0.1	1000 ± 44	4000 ± 53	17 70
S21767	OCH_3	CH_3	64 ± 1	0,6 ± 0.02	0,7 ± 0.01	1/103 1/92
6a	$COOCH_3$	CH_3	14 ± 0.9	nd[a]	nd[a]	— —
6b	$COOCH_3$	$CH(CH_3)_2$	65 ± 1	nd[a]	nd[a]	— —
6d	$COOCH_3$	*c*-C_5H_9	18 ± 1.1	3880 ± 42	389 ± 6	215 21.6
6e	$COOCH_3$	2-Furyl	53 ± 1	>10,000	>10,000	>188 >188
7a	$CONH_2$	CH_3	82 ± 0.5	>10,000	1000 ± 41	122 12
7e	$CONH_2$	2-Furyl	67 ± 0.8	>10,000	>10,000	>149 >149
8a	$CONHCH_3$	CH_3	12 ± 0.3	189 ± 5	>1000	16 >83
8c	$CONHCH_3$	*c*-C_3H_5	41 ± 1.1	1220 ± 10	>10,000	>29 >244
8d	$CONHCH_3$	*c*-C_5H_9	nd[a]	>10,000	>10,000	— —
10a	$NHCOOCH_3$	CH_{30}	16 ± 0.4	nd[a]	nd[a]	— —
10b	$NHCOOCH_3$	$CH(CH_3)_2$	23 ± 0.3	5350 ± 32	4580 ± 12	232 199
10c	$NHCOOCH_3$	*c*-C_3H_5	24 ± 1.1	8180 ± 5	5900 ± 22	340 245
10d	$NHCOOCH_3$	*c*-C_5H_9	nd[a]	5320 ± 19	5320 ± 29	— —
10e	$NHCOOCH_3$	2-Furyl	56 ± 1.5	>10,000	>10,000	>178 >178
10f	$NHCOOCH_3$	$CH_2CH{=}CH_2$	11 ± 0.9	2690 ± 21	560 ± 11	244 51
11	$NHCOCF_3$	CH_3	nd[a]	>10,000	2000 ± 54	— —

[a] nd, not determined.

2.2. Pharmacology

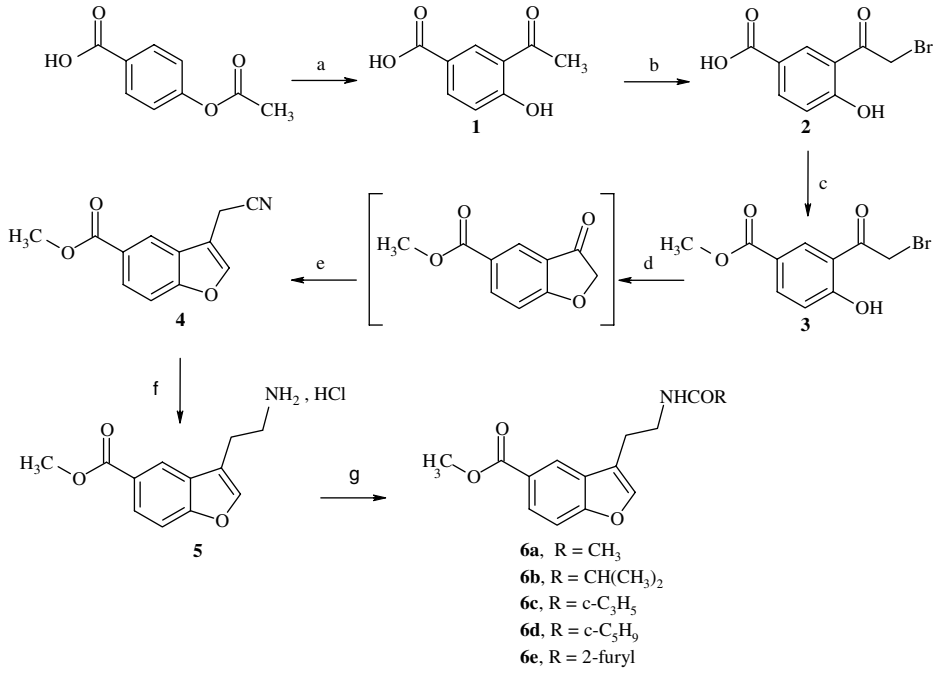
The affinities of the compounds for the melatonin receptor subtypes were evaluated *in vitro* in binding assays using 2-[^{125}I]-iodomelatonin, human embryonic kidney cell line HEK293 stably expressing MT_1 or MT_2 human melatonin receptors, and hamster brain membrane preparations for the MT_3 binding site according to a previously described method.[22]

The chemical structures, binding affinities (MT_1, MT_2, and MT_3), and selectivity ratios of the new compounds are reported in Table 1.

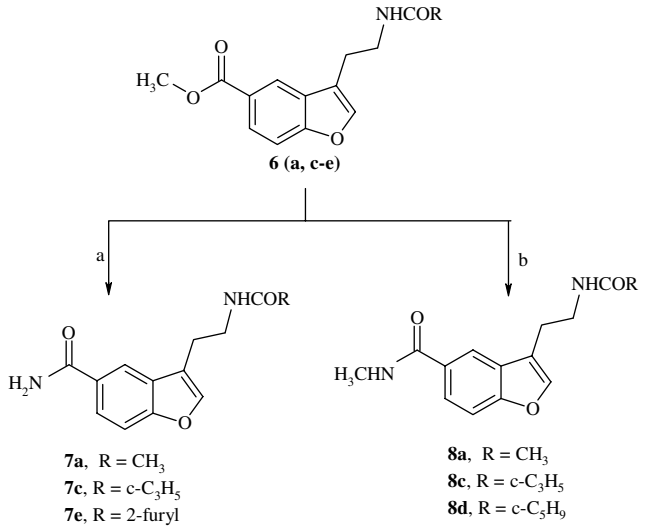
The benzofurane bioisostere of melatonin (**S21767**) can be considered a very interesting lead compound: (i) its affinity values for both MT_1 and MT_2 receptors and MT_3 binding site are nearly the same as those of melatonin (Table 1), and (ii) its predicted bioavailability is better than that of melatonin.

Starting from this benzofuranic bioisostere, we decided to incorporate changes at the C-5 positions and in the acyl side chain to investigate structure–affinity-selectivity relationships for MT_1, MT_2, and MT_3 subtypes.

The positive effect of a 5-methoxycarbonylamino (carbamate) substitution toward MT_3 selectivity has already been described for melatonin itself. It is also observed in our series and affects both MT_1, MT_2, and MT_3 subtypes, leading to a MT_3 selective ligand (**10a**; Table 1). Further structural variations at the *N*-acyl group were found to be important. Replacement of the methyl



Scheme 1. Synthesis of esters **6a**–**e**. [a]Reagents: (a) $AlCl_3$, $C_6H_5NO_2$; (b) Br_2, CH_3COOH; (c) $SOCl_2$, CH_3OH; (d) K_2CO_3, acetone; (e) $(C_2H_5O)_2P(O)CH_2CN$, NaH, THF; (f) H_2, PtO_2, $CHCl_3/CH_3OH$; (g) ClCOR, $N(Et)_3$, CH_2Cl_2.



Scheme 2. Synthesis of amides **7**(**a**, **c**, **e**) and **8**(**a**, **c**, **d**). [a]Reagents: (a) NH_4OH 20%/H_2O (Method A) or (i) $HCONH_2$, DMF, (ii) CH_3ONa (Method B); (b) CH_3NH_2, CH_3OH.

group of the amide side chain by an isopropyl (**10b**), cyclopropyl (**10c**), furyl (**10e**) or allyl (**10f**) does not modify the binding affinity for the MT_3 binding site. Nevertheless, these modifications sharply decrease the binding affinity for both MT_1 and MT_2, thus increasing the MT_3 selectivity.

Replacement of the carbamate group on the 5-position by ester group (**6**), primary or secondary amide group (**7**, **8**) decreases the MT_3 selectivity except when a furyl heterocycle is grafted on the *N*-acyl chain (**6e**, **7e**).

3. Conclusions

Introduction of a methoxycarbonylamino group in the C-5 benzofuran position allows access to MT_3 selective ligands, and modulation of the selectivity can be obtained with suitable modification on the *N*-acyl substituents.

The most selective compounds **10b** and **10c** show MT_1/MT_3 and MT_2/MT_3 selectivity ratios of 232/199 and 340/245, respectively. These ratios are noticeably higher than that of MCANAT itself (S = 17/70).

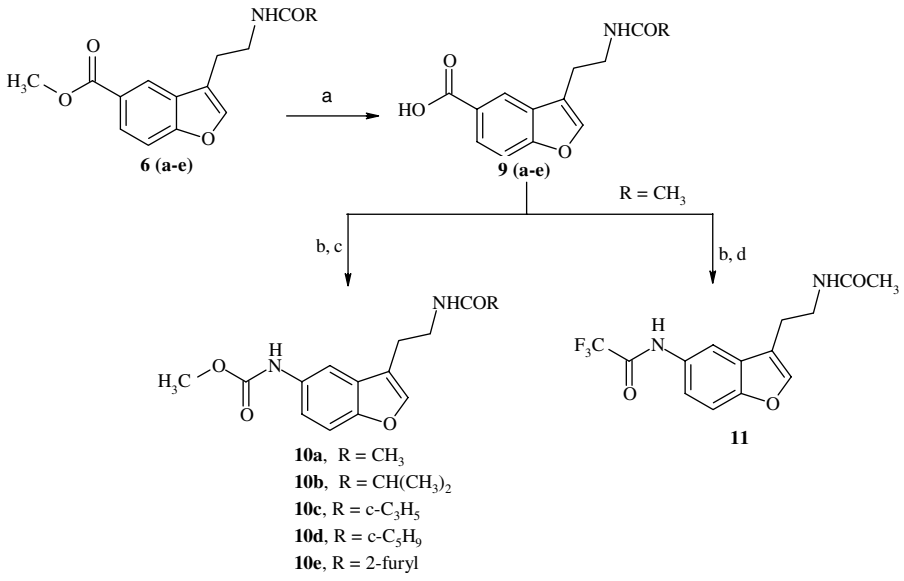
4. Experimental

4.1. Chemistry

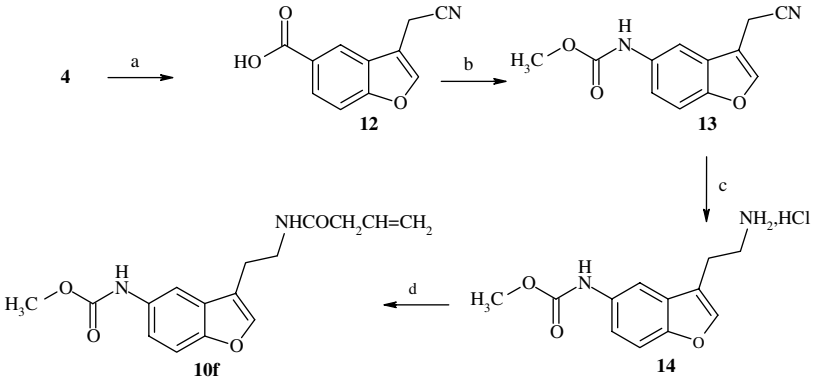
Melting points were determined on a Buchi SMP-20 capillary apparatus and are uncorrected. IR spectra were recorded on a Vector 22 Bruker spectrophotometer. ^{1}H NMR spectra were recorded on a AC 300 Bruker spectrometer. Chemical shifts are reported in δ units (parts per million) relative to $(Me)_4Si$. HR-FAB/MS were recorded on a JEOL LMS-SX/SX 102A.

Compound purity and Mass spectra were performed on Surveyor MSQ Thermoelectron spectrometer (+cAPCI corona sid = 30.00, det = 1400.00 Full ms [100.00–1000.00]) Elemental analyses for final substances were performed by CNRS Laboratories (Vernaison, France). Obtained results were within 0.4% of the theoretical values.

4.1.1. 3-Bromoacetyl-4-hydroxybenzoic acid (2). Compound **1** (5.8 g, 0.032 mol) was added to a solution of



Scheme 3. Synthesis of compounds **10** (**a**–**e**) and **11**. [a]Reagents: (a) i—NaOH, CH_3OH, H_2O; ii—6 M HCl; (b) i—ClCOOEt, $N(Et)_3$, acetone; ii—NaN_3, H_2O; (c) CH_3OH/Toluene, reflux; (d) TFA, CH_2Cl_2.



Scheme 4. Synthesis of compound **10f**. [a]Reagents: (a) i—NaOH, MeOH, H_2O; ii—6 M HCl; (b) i—ClCOOEt, $N(Et)_3$, acetone; ii—NaN_3, H_2O; iii—CH_3OH/Toluene, reflux; (c) i—H_2, Raney nickel, CH_3OH; ii—HCl(g); (d) $CH_2{=}CHCH_2COOH$, EDCI, HOBT, CH_2Cl_2.

bromine (2.5 mL, 0.048 mol) in 40 mL of glacial acetic acid. After stirring at 80 °C for 2 h, the reaction mixture was poured into ice-cold water. The precipitate was filtered, washed with water, dried, and crystallized from ethanol 95° to give 6.7 g (80% yield) of **2**; mp 174–175 °C; MS (APCI, pos. 30 V) *m/z*: $[M+H]^+$ 260; IR (neat, cm^{-1}) 3502–3400, 1689, 1653, 1224; ^1H NMR (DMSO-d_6) δ 4.94 (s, 2H), 7.09 (d, $J = 8.7$ Hz, 1H), 8.02 (dd, $J = 8.7$ and 1.8 Hz, 1H), 8.33 (d, $J = 1.8$ Hz, 1H), 11.80 (s, 1H), 12.23 (s, 1H).

4.1.2. Methyl-(3-bromoacetyl-4-hydroxy)benzoate (3). Thionyl chloride (4.0 mL, 0.055 mol) was added dropwise to a solution of **2** (7.1 g, 0.027 mol) in 70 mL of methanol cooled to 0 °C. After stirring at room temperature for 1 h, the reaction mixture was refluxed for 2 h, then concentrated under reduced pressure. The residue was extracted off with ethyl acetate, washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a residue which was recrystallized from isopropanol to give 5.3 g (70% yield) of **3**; mp 93–94 °C; MS (APCI, pos. 30 V) *m/z*: $[M+H]^+$ 274; IR (neat, cm^{-1}) 3580–3250, 1710, 1662, 1220, 1174, 1114; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (s, 3H), 4.54 (s, 2H), 7.08 (d, $J = 8.9$ Hz, 1H), 8.19 (dd, $J = 8.9$ and 2.2 Hz, 1H), 8.50 (d, $J = 2.2$ Hz, 1H), 9.45 (s, 1H).

4.1.3. (5-Methoxycarbonyl-3-benzo[*b*]furan-3-yl)acetonitrile (4). A mixture of **3** (4.1 g, 0.015 mol) and K_2CO_3 (4.1 g, 0.030 mol) in 35 mL of acetone was stirred at room temperature for 2 h. The precipitate was filtered and washed with acetone. The filtrate was then concentrated under reduced pressure to give an intermediate benzofuranone which was not isolated.

Under stirring and N_2, diethyl cyanomethylphosphonate (3.5 mL, 0.023 mol) in 30 mL of anhydrous THF was added dropwise at −10 °C to a mixture of NaH (0.9 g, 0.023 mol) (60% in mineral oil) in 40 mL of anhydrous THF. After 1 h, the intermediate benzofuranone in 70 mL of anhydrous THF was added dropwise at −10 °C, then the stirring was continued at room temperature for 2 h. The mixture was poured into cold water

and extracted with diethyl ether. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The oily residue was purified by column chromatography (SiO_2, CH_2Cl_2) to afford a yellow solid. Recrystallization from absolute ethanol gave 1.6 g (50% yield) of **4**; mp 125–126 °C; MS (APCI, pos. 30 V) *m/z*: $[M+H]^+$ 216; IR (neat, cm^{-1}) 2250, 1717, 1287, 1259, 1190; ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 2H), 3.96 (s, 3H), 7.55 (d, $J = 8.5$ Hz, 1H), 7.75 (s, 1H), 8.09 (dd, $J = 8.5$ and 1.7 Hz, 1H), 8.31 (d, $J = 1.7$ Hz, 1H).

4.1.4. *N*-2-(5-Methoxycarbonyl-benzo[*b*]furan-3-yl)ethylamine hydrochloride (5). A solution of **4** (0.70 g, 0.003 mol) in 30 mL of methanol and 3 mL of chloroform was hydrogenated over PtO_2 (0.11 g, 0.004 mol) under pressure (35 bars) at room temperature for 48 h. After filtration and evaporation, the residue was recrystallized from acetonitrile to give 0.72 g (86% yield) of **5**; mp 210–211 °C; MS (APCI, pos. 30 V) *m/z*: $[M+H]^+$ 220; IR (neat, cm^{-1}) 3500–3400, 1710, 1300, 1249, 1188; ^1H NMR (300 MHz, DMSO-d_6) δ 3.07 (t, $J = 4.5$ Hz, 2H), 3.36 (m, 2H), 3.89 (s, 3H), 7.71 (d, $J = 8.7$ Hz, 1H), 7.97 (dd, $J = 8.7$ and 1.8 Hz, 1H), 8.06 (s, 1H), 8.10–8.23 (br s, 3H), 8.35 (d, $J = 1.8$ Hz, 1H).

4.2. General procedure for the preparation of amides (6a–e)

Triethylamine (0.002 mol) was added to a solution of **5** (0.001 mol) in 30 mL of anhydrous methylene chloride. After stirring for 10 min at 0 °C, 0.001 mol of the appropriate acid chloride was added dropwise at this temperature. The reaction mixture was stirred at room temperature for 20 min. The organic phase was separated, washed with a 1 M HCl solution and water, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the desired amides (**6a**–**e**).

4.2.1. *N*-(2-(5-Methoxycarbonyl-benzo[*b*]furan-3-yl)ethyl)-acetamide (6a). Recrystallized from cyclohexane; yield 43%; mp 121–122 °C; IR (neat, cm^{-1}) 3260, 1705, 1640; ^1H NMR (300 MHz, DMSO-d_6) δ 1.80 (s, 3H), 2.73 (t, $J = 6.9$ Hz, 2H), 3.32 (m, 2H), 3.92 (s, 3H), 7.32 (dd, $J = 8.8$ and 1.7 Hz, 1H), 7.45 (d, $J = 8.8$ Hz, 1H), 7.77 (s, 1H), 7.79 (d, $J = 1.7$ Hz, 1H), 8.01 (t, $J = 5.4$ Hz, 1H); Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64,36; H, 5.79; N, 5.36. Found: C, 64.14; H, 5.81; N, 5.28.

4.2.2. *N*-(2-(5-Methoxycarbonyl-benzo[*b*]furan-3-yl)ethyl)-isopropylcarboxamide (6b). Recrystallized from cyclohexane/toluene (1:3); yield 65%; mp 98–100 °C; IR (neat, cm^{-1}) 3290, 1710, 1633; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (d, $J = 6.7$ Hz, 6H), 2.30 (m, 1H), 2.94 (t, $J = 6.8$ Hz, 2H), 3.61 (m, 2H), 3.94 (s, 3H), 5.57 (t, $J = 5.6$ Hz, 1H), 7.49 (d, $J = 8.7$ Hz, 1H), 7.52 (s, 1H), 8.04 (dd, $J = 8.7$ and 1.8 Hz, 1H), 8.29 (d, $J = 1.8$ Hz, 1H). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.38; H, 6.40; N, 4.62.

4.2.3. *N*-(2-(5-Methoxycarbonyl-benzo[*b*]furan-3-yl)ethyl)-cyclopropylcarboxamide (6c). Recrystallized from ethanol; yield 55%; mp 154–155 °C; IR (neat, cm^{-1}) 3257, 1709, 1643, 1325, 1253, 1182; ^1H NMR (300 MHz, DMSO-d_6) δ 0.58–0.79 (m, 4H), 1.47 (m, 1H), 3.10–3.32 (m, 4H), 3.86 (s, 3H), 7.67 (d, $J = 8.6$ Hz, 1H), 7.92 (dd, $J = 8.6$ and 1.3 Hz, 1H), 7.93 (m, 1H), 8.21 (t, $J = 5.6$ Hz, 1H), 8.26 (d, $J = 1.3$ Hz, 1H). Anal. Calcd for $C_{16}H_{17}NO_4$: C,66.89; H, 5.96; N, 4.87. Found: C, 66.78; H, 5.92; N 4.75.

4.2.4. *N*-(2-(5-Methoxycarbonyl-benzo[*b*]furan-3-yl)ethyl)-cyclopentylcarboxamide (6d). Recrystallized from toluene; yield 67%; mp 122–123 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.43–1.75 (m, 8H), 2.50 (s, 1H), 2.84 (t, $J = 6.9$ Hz, 2H), 3.36 (m, 2H), 3.90 (s, 3H), 7.68 (d, $J = 8.5$ Hz, 1H), 7.80–8.00 (m, 3H), 8.30 (d, $J = 1.1$ Hz, 1H). IR (neat, cm^{-1}) 3258, 1718, 1631. Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C,68.42; H,6.72; N, 4.36.

4.2.5. *N*-(2-(5-Methoxycarbonyl-benzo[*b*]furan-3-yl)ethyl)-furoylamide (6e). Recrystallized from isopropanol; yield 70%; mp 116–118 °C; IR (neat, cm^{-1}) 3275, 1713, 1660, 1645; ^1H NMR (300 MHz, DMSO-d_6) δ 2.93 (t, $J = 7.1$ Hz, 2H), 3.51 (m, 2H), 3.85 (s, 3H), 6.60 (m, 1H), 7.05 (d, $J = 3.2$ Hz, 1H), 7.66 (d, $J = 8.6$ Hz, 1H), 7.81 (m, 1H), 7.92 (dd, $J = 8.6$ and 1.6 Hz, 1H), 7.97 (s, 1H), 8.31 (m, 1H), 8.56 (t, $J = 5.6$ Hz, 1H). Anal. Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H,4.83; N, 4.47. Found: C, 64.80; H, 4.84; N, 4.50.

4.2.6. *N*-(2-(5-Carboxamido-benzo[*b*]furan-3-yl)ethyl)-acetamide (7a)

4.2.6.1. Method A. A solution of **6a** (26.2 g, 0.1 mol) in 50 mL of aqueous 20% ammonia was refluxed under stirring for 5 h. The reaction mixture was cooled and concentrated under reduced pressure. Recrystallization from ethanol gave 10.6 g (43% yield) of **7a**.

4.2.6.2. Method B. Formamide (0.68 mL, 0.015 mol) was added to a solution of **6a** (0.39 g, 0.0015 mol) in DMF (10 mL). After 15 min of stirring at 80 °C, a 30% solution of sodium (0.006 at.gr) in methanol was added, and then the mixture was refluxed overnight. After cooling, the reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was recrystallized from ethanol 95° to afford 0.19 g (50% yield) of **7a**; mp 206–208 °C; IR (neat, cm^{-1}) 3288, 1662, 1620; ^1H NMR (300 MHz, DMSO-d_6) δ 1.79 (s, 3H), 2.81 (t, 2H, $J = 6.6$ Hz), 3.39 (m, 2H), 7.35 (s, 1H), 7.61 (d, $J = 8.5$ Hz, 1H), 7.83–7.87 (m, 2H), 8.01 (m, 2H), 8.22 (d, $J = 1.5$ Hz, 1H). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.23; H, 5.89; N, 11.17.

4.2.7. *N*-(2-(5-Methylcarbamoyl-benzo[*b*]furan-3-yl)ethyl)-furylcarboxamide (7e). This compound was prepared from **6e** according to the procedure (Method A) described for **7a**. Recrystallized from ethyl acetate; yield 40%; mp 110–112 °C; IR (neat, cm^{-1}) 3350, 3426, 1664, 1624; ^1H NMR (300 MHz, DMSO-d_6) δ 2.94 (t, $J = 6.7$ Hz, 2H), 3.57 (m, 2H), 6.62 (m, 1H), 7.09 (m, 1H), 7.36 (s, 1H), 7.59 (dd, $J = 8.1$ and 1.2 Hz, 1H),

7.84–7.93 (m, 3H), 8.02 (s, 1H), 8.28 (m, 1H), 8.57 (t, J = 5.5 Hz, 1H). Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.23; H, 4.98; N, 9.25.

4.2.8. *N*-(2-(5-Methylcarbamoyl-benzo[*b*]furan-3-yl)ethyl)-acetamide (8a). A 40% aqueous solution of methylamine (1.6 mmol) was added to a solution of ester **6a** (0.26 g, 0.001 mol) in 40 mL of methanol. The mixture was refluxed for 2 h, cooled to room temperature, concentrated under reduced pressure, then extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was recrystallized from toluene to give 0.11 g (43% yield) of **8a**; mp 158–159 °C; IR (neat, cm^{-1}) 3262, 1665, 1630; ^1H NMR (300 MHz, DMSO-d_6) δ 1.80 (s, 3H), 2.79–2.83 (m, 5H), 3.36 (m, 2H), 7.60 (d, J = 8.5 Hz, 1H), 7.81 (dd, J = 8.5 and 1.9 Hz, 1H), 7.89 (s, 1H), 8.00 (t, J = 5.1 Hz, 1H), 8.16 (d, J = 1.9 Hz, 1H), 8.48 (q, J = 3.1 Hz, 1H). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H,6.20; N, 10.76. Found: C, 64.27; H, 6.13; N, 10.44.

4.2.9. *N*-(2-(5-Methylcarbamoyl-benzo[*b*]furan-3-yl)ethyl)-cyclopropylcarboxamide (8c). This compound was prepared from **6c** according to the procedure described for **8a**. Recrystallized from water; yield 41%; mp 188–189 °C; IR (neat, cm^{-1}) 3265, 1659, 1629; ^1H NMR (300 MHz, DMSO-d_6) δ 0.58–0.69 (m, 4H), 1.50 (m, 1H), 2.80–2.82 (m, 5H), 3.41 (m, 2H), 7.60 (d, J = 8.2 Hz, 1H), 7.80 (dd, J = 8.2 and 1.5 Hz, 1H), 7.87 (s, 1H), 8.15 (d, J = 1.5 Hz, 1H), 8.22 (t, J = 5.5 Hz, 1H), 8.47 (q, J = 4.2 Hz, 1H). Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.00; H, 6.34; N, 9.77.

4.2.10. *N*-(2-(5-Methylcarbamoyl-benzo[*b*]furan-3-yl)ethyl)-cyclopentylcarboxamide (8d). This compound was prepared from **6d** according to the procedure described for **8a**. Recrystallized from toluene; yield 40%; mp 170–171 °C; IR (neat, cm^{-1}) 3265, 1652, 1630; ^1H NMR (300 MHz, DMSO-d_6) δ 1.46–1.71 (m, 8H), 2.50 (s, 1H), 2.81 (m, 2H), 3.34 (m, 3H), 3.39 (m, 2H), 7.59 (d, J = 8.7 Hz, 1H), 7.80 (dd, J = 8.7 and 1.4 Hz, 1H), 7.86 (s, 1H), 7.91 (t, J = 5.4 Hz, 1H), 8.15 (d, J = 1.4 Hz, 1H), 8.47 (q, J = 4.5 Hz, 1H). Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.54; H, 7.10; N, 8.88.

4.2.11. *N*-(2-(5-Carboxy-benzo[*b*]furan-3-yl)ethyl)acetamide (9a). A 30% NaOH aqueous solution (30 mL) was added to a solution of ester **6a** (0.52 g, 0.002 mol) in 90 mL of methanol. The mixture was stirred overnight at room temperature, then the solvent was evaporated under reduced pressure. The aqueous residue was cooled to 0 °C, acidified with a 6 M HCl solution and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was recrystallized from ethanol 95° to give 0.46 g (93% yield) of **9a**; mp 210–211 °C; MS (APCI, pos. 30 V) m/z: $[M+H]^+$ 248; IR (neat, cm^{-1}) 3536, 2440, 1688, 1637; ^1H NMR (300 MHz, DMSO-d_6) δ 1.80 (s, 3H), 2.71 (t, J = 6.1 Hz, 2H), 3.34 (m, 2H), 7.30 (dd, J = 8.8 and 1.8 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.78 (s, 1H), 7.81 (d, J = 1.8 Hz, 1H), 8.05 (br s, 1H), 12.40 (br s, 1H).

4.2.12. *N*-(2-(5-Carboxy-benzo[*b*]furan-3-yl)ethyl)isopropylcarboxamide (9b). This compound was prepared from **6b** according to the procedure described for **9a**. Recrystallized from ethanol 95°/water (1:1); yield 96%; mp 200–202 °C; MS (APCI, pos. 30 V) m/z: $[M+H]^+$ 276; IR (neat, cm^{-1}) 3490, 3298, 1683, 1641; ^1H NMR (300 MHz, DMSO-d_6) δ 0.97 (d, J = 6.8 Hz, 6H), 2.30 (m, 1H), 2.82 (t, J = 6.9 Hz, 2H), 3.34 (m, 2H), 7.64 (d, J = 8.3 Hz, 1H), 7.90 (m, 2H), 8.28 (m, 1H), 8.05 (br s, 1H), 12.88 (br s, 1H).

4.2.13. *N*-(2-(5-Carboxy-benzo[*b*]furan-3-yl)ethyl)cyclopropylcarboxamide (9c). This compound was prepared from **6c** according to the procedure described for **9a**. Recrystallized from ethanol 95°; yield 93%; mp 128–130 °C; MS (APCI, pos. 30 V) m/z: $[M+H]^+$ 274; IR (neat, cm^{-1}) 3497, 2462, 1691, 1645; ^1H NMR (300 MHz, DMSO-d_6) δ 0.62–0.68 (m, 4H), 1.51 (m, 1H), 3.37–3.42 (m, 4H), 7.66 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.95 (s, 1H), 8.25 (t, J = 6.0 Hz, 1H), 8.29 (m, 1H), 12.88 (br s, 1H).

4.2.14. *N*-(2-(5-Carboxy-benzo[*b*]furan-3-yl)ethyl)cyclopentylcarboxamide (9d). This compound was prepared from **6d** according to the procedure described for **9a**. Recrystallized from ethanol 95°/water (1:1); yield 95 %; mp 208–210 °C; MS (APCI, pos. 30 V) m/z: $[M+H]^+$ 302; IR (neat, cm^{-1}) 3500, 3290, 1680, 1630; ^1H NMR (300 MHz, DMSO-d_6) δ 1.42–1.80 (m, 8H), 2.50 (m, 1H), 2.82 (t, J = 6.9 Hz, 2H), 3.35 (m, 2H), 7.63 (d, J = 8.6 Hz, 1H), 7.90–7.95 (m, 3H), 8.27 (d, J = 1.7 Hz, 1H), 12.87 (s, 1H).

4.2.15. *N*-(2-(5-Carboxy-benzo[*b*]furan-3-yl)ethyl)furylcarboxamide (9e). This compound was prepared from **6e** according to the procedure described for **9a**. Recrystallized from ethanol 95°/water (1:1); yield 90 %; mp 220–222 °C; MS (APCI, pos. 30 V) m/z: $[M+H]^+$ 300; IR (neat, cm^{-1}) 3913, 1696, 1646; ^1H NMR (300 MHz, DMSO-d_6) δ 2.93 (t, J = 6.9 Hz, 2H), 3.53 (m, 2H), 6.60 (m, 1H), 7.06 (d, J = 3.3 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.81 (m, 1H), 7.92 (dd, J = 8.4 and 1.5 Hz, 1H), 7.95 (s, 1H), 8.32 (d, J = 1.5 Hz, 1H), 8.57 (t, J = 5.7 Hz, 1H), 12.87 (s, 1H). Anal. Calcd for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.12; H, 4.52, N, 4.55.

4.2.16. *N*-(2-(5-Methoxycarbonylamino-benzo[*b*]furan-3-yl)ethyl)acetamide (10a). Triethylamine (0.2 mL, 0.015 mol) and ethyl chloroformate (1.5 mL, 0.015 mol) were added at 0 °C to a stirred solution of acid **9a** (2.47 g, 0.01 mol) in 50 mL of acetone. After 1 h of stirring at 0 °C, sodium azide (1 g, 0.015 mol) dissolved in 1 mL of water was added, then the mixture was stirred at room temperature for 1 h, poured into water and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, affording the intermediate *N*-(2-(5-azidocarbonyl-benzo[*b*]furan-3-yl)ethyl) acetamide. This crude azide was dissolved

in 50 mL of absolute ethanol and 50 mL of toluene. The solution was refluxed overnight, then the solvents were evaporated under reduced pressure. The residue was recrystallized from toluene to give 0.72 g (26% yield) of **10a**; mp 138–140 °C; IR (neat, cm^{-1}) 3312, 1704, 1635, 1248, 1057; ^1H NMR (300 MHz, DMSO-d_6) δ 1.81 (s, 3H), 2.73 (t, J = 6.9 Hz, 2H), 3.35 (m, 2H), 3.67 (s, 3H), 7.31 (d, J = 9.0 Hz, 1H), 7.44 (d, J = 9.0 Hz, 1H), 7.76–7.80 (m, 2H), 8.01 (t, J = 5.9 Hz, 1H), 9.65 (s, 1H). Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.92; H, 5.74; N, 10.24.

4.2.17. *N*-(2-(5-Methoxycarbonylamino-benzo[*b*]furan-3-yl)ethyl)isopropylcarboxamide (10b). This compound was prepared from **9b** according to the procedure described for **10a**. The intermediate azide was not isolated. Recrystallized from toluene/cyclohexane (2:1); yield 65%; mp 122–124 °C; IR (neat, cm^{-1}) 3314, 1703, 1639; ^1H NMR (300 MHz, DMSO-d_6) δ 0.98 (d, J = 6.6 Hz, 6H), 2.28–2.35 (m, 1H), 2.73 (t, J = 6.9 Hz, 2H), 3.32 (m, 2H), 3.68 (s, 3H), 7.30 (dd, J = 8.4 and 1.1 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.74 (s, 1H), 7.79 (d, J = 1.1 Hz, 1H), 7.89 (t, J = 5.5 Hz, 1H), 9.64 (s, 1H). Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.59; H, 6.62; N, 9.26.

4.2.18. *N*-(2-(5-Methoxycarbonylamino-benzo[*b*]furan-3-yl)ethyl)cyclopropylcarboxamide (10c). This compound was prepared from **9c** according to the procedure described for **10a**. The intermediate azide was not isolated. Purified by column chromatography (SiO_2, CH_2Cl_2/ethyl acetate 1:1) and recrystallized from toluene; yield 26%; mp 153–155 °C; IR (neat, cm^{-1}) 3329, 1705, 1642, 1244, 1055; ^1H NMR (300 MHz, DMSO-d_6) δ 0.58–0.69 (m, 4H), 1.52 (m, 1H), 2.75 (t, J = 7.2 Hz, 2H), 3.36 (m, 2H), 3.68 (s, 3H), 7.29 (d, J = 8.9 Hz, 1H), 7.46 (d, J = 8.9 Hz, 1H), 7.76 (m, 2H), 8.22 (m, 1H), 9.64 (s, 1H). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.27; H, 6.02; N, 9.14.

4.2.19. *N*-(2-(5-Methoxycarbonylamino-benzo[*b*]furan-3-yl)ethyl)cyclopentylcarboxamide (10d). This compound was prepared from **9d** according to the procedure described for **10a**. The intermediate azide was not isolated. Purified by column chromatography (SiO_2, ethyl acetate) and recrystallized from toluene/cyclohexane (2:1); yield 70%; mp 147–148 °C; IR (neat, cm^{-1}) 3329, 1705, 1642, 1244, 1055; ^1H NMR (300 MHz, DMSO-d_6) δ 1.42–1.72 (m, 8H), 2.50 (m, 1H), 2.72 (t, J = 7.0 Hz, 2H), 3.33 (m, 2H), 3.68 (s, 3H), 7.27 (dd, J = 9.0 and 2.0 Hz, 1H), 7.44 (d, J = 9.0 Hz, 1H), 7.74 (s, 1H), 7.77 (m, 1H), 7.92 (t, J = 5.5 Hz, 1H), 9.63 (s, 1H). Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.50; H, 6.72; N, 8.26.

4.2.20. *N*-(2-(5-Methoxycarbonylamino-benzo[*b*]furan-3-yl)ethyl)furylcarboxamide (10e). This compound was prepared from **9e** according to the procedure described for **10a**. The intermediate azide was not isolated. Purified by column chromatography (SiO_2, ethyl acetate) and recrystallized from toluene/cyclohexane (3:1); yield 26%; mp 119–121 °C; IR (neat, cm^{-1}) 3260, 3254, 1713, 1647, 1240, 1076; ^1H NMR (300 MHz, DMSO-d_6) δ 2.85 (t, J = 6.7 Hz, 2H), 3.51 (m, 2H), 6.67 (s, 3H), 6.61 (m, 1H), 7.07 (d, J = 3.2 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.80 (m, 3H), 8.56 (t, J = 4.9 Hz, 1H), 9.64 (s, 1H). Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.05; H, 4.85; N, 8.44.

4.2.21. *N*-(2-(5-Trifluoroacetamido-benzo[*b*]furan-3-yl)ethyl)-acetamide (11). Triethylamine (0.4 mL, 0.030 mol) and ethyl chloroformate (3.0 mL, 0.030 mol) were added at 0 °C to a stirred solution of acid **9a** (4.94 g, 0.020 mol) in 80 mL of acetone. After 1 h of stirring at 0;°C, sodium azide (2 g, 0.030 mol) dissolved in 2 mL of water was added, then the mixture was stirred at room temperature for 1 h, poured into water and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, affording the intermediate azide which was immediately dissolved in 70 mL of methylene chloride. Trifluoroacetic acid (18.2 mL, 0.023 mol) was added and the mixture was stirred at room temperature overnight, washed with water and with a 10% $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The oily residue was purified by column chromatography (SiO_2, ethyl acetate) to afford a brown solid. Recrystallization from ethyl acetate gave 3.27 g (65% yield) of **11**; mp 152–154 °C; IR (neat, cm^{-1}) 3340, 1695, 1645, 1150; ^1H NMR (300 MHz, DMSO-d_6) δ 1.79 (s, 3H), 2.76 (t, J = 6.9 Hz, 2H), 3.32 (m, 2H), 7.52 (dd, J = 8.1 and 1.9 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.86 (s, 1H), 7.95 (d, J = 1.9 Hz, 1H), 8.01 (t, J = 5.4 Hz, 1H), 11.32 (s, 1H). Anal. Calcd for $C_{14}H_{13}F_3N_2O_3$: C, 53.51; H, 4.17; N, 8.91. Found: C, 53.23; H, 4.22; N, 9.05.

4.2.22. *N*-(2-(5-Carboxy benzo[*b*]furan-3-yl)ethyl)acetonitrile (12). A 10% K_2CO_3 aqueous solution (40 mL) was added to a solution of nitrile **4** (0.73 g, 0.0034 mol) in 60 mL of methanol. The mixture was stirred 48 h at room temperature, then the solvent was evaporated under reduced pressure. The aqueous residue was cooled to 0 °C, acidified with a 6 M HCl solution and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was recrystallized from ethanol 95°/water (1:1) to give 0.58 g (85% yield) of **12**; mp 199–201 °C; MS (APCI, pos. 30 V) m/z: $[M+H]^+$ 202; IR (neat, cm^{-1}) 3400–3250, 2250, 1680; ^1H NMR (300 MHz, DMSO-d_6) δ 4.21 (m, 2H), 7.73 (d, J = 8.8 Hz, 1H), 7.99 (dd, J = 8.8 and 1.4 Hz, 1H), 8.14 (s, 1H), 8.37 (d, J = 1.4 Hz, 1H), 13.03 (s, 1H).

4.2.23. *N*-(2-(5-Methoxycarbonylamino-benzo[*b*]furan-3-yl) ethyl)acetonitrile (13). Triethylamine (0.6 mL, 0.0045 mol) and ethyl chloroformiate (0.4 mL, 0.0045 mol) were added at 0 °C to a stirred solution of acid **12** (0.6 g, 0.003 mol) in 50 mL of acetone. After 1 h of stirring at 0 °C, sodium azide (0.3 g, 0.0045 mol) dissolved in 1 mL of water was added, then the mixture was stirred at room temperature for 1 h, poured into water and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered,

and concentrated under reduced pressure, affording the intermediate azide which was not isolated. It was dissolved immediately in 40 mL of methanol and 40 mL of toluene. The solution was heated at 80 °C overnight, then the solvents were evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, ethyl acetate) to afford 0.49 g (72% yield) of **13** as a yellow solid; mp 102–104 °C; MS (APCI, pos. 30 V) *m/z*: $[M+H]^+$ 231; IR (neat, cm^{-1}) 3342, 2250, 1717; ^1H NMR (300 MHz, DMSO-d_6) δ 3.67 (s, 3H), 4.10 (s, 2H), 7.35 (dd, $J = 8.8$ and 1.3 Hz, 1H), 7.54 (d, $J = 8.8$ Hz, 1H), 7.88 (d, $J = 1.3$ Hz, 1H), 7.96 (s, 1H), 9.74 (s, 1H).

4.2.24. *N*-2-(5-Methoxycarbonylamino-benzo[*b*]furan-3-yl)ethylamine hydrochloride (14). A solution of **13** (0.50 g, 0.0022 mol) in 30 mL of methanol and 3 mL of chloroforme was hydrogenated over PtO_2 (0.10 g, 0.0003 mol) under pressure (35 bars) at room temperature for 24 h. After filtration and evaporation, the residue was recrystallized from acetonitrile to give 0.40 g (68% yield) of **14**; mp > 230°C; MS (APCI, pos. 30 V) *m/z*: $[M+H]^+$ 235; IR (neat, cm^{-1}) 3420–3200, 1700; ^1H NMR (300 MHz, DMSO-d_6) δ 2.95 (t, $J = 7.8$ Hz, 2H), 3.09 (s, 2H), 3.68 (s, 3H), 7.29 (dd, $J = 8.7$ and 2.0 Hz, 1H), 7.49 (d, $J = 8.7$ Hz, 1H), 7.80–7.89 (m, 2H), 8.15 (br s, 3H), 9.70 (s, 1H).

4.2.25. *N*-(2-(5-Methoxycarbonylamino-benzo[*b*]furan-3-yl)ethyl)vinylacetamide (10f). A solution of vinylacetic acid (0.1 mL, 0.0013 mol) in 50 mL of methylene chloride was stirred at −10 °C for 20 min. Then, triethylamine (0.023 mL, 0.0017 mol), EDCI (0.3 g, 0.0014 mol) and HOBt (0.2 g, 0.0014 mol) were added, and the mixture was stirred at −10 °C for 30 min. A solution of **14** (0.50 g, 0.0019 mol) in 10 mL of methylene chloride was cooled at −10 °C and added dropwise. After 4 days of stirring at room temperature, the reaction mixture was washed with water, a 1 M HCl solution, water, a 10% NaOH solution, and water until pH 7 was reached. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, ethyl acetate) to afford a white solid. Recrystallization from toluene/cyclohexane (2:1) gave 0.12 g (20% yield) of **10f**; mp 145–146 °C; IR (neat, cm^{-1}) 3420–3200, 1700; ^1H NMR (300 MHz, DMSO-d_6) δ 2.74 (t, $J = 7.2$ Hz, 2H), 2.88 (d, $J = 7.0$ Hz, 2H), 3.39 (t, $J = 7.2$ Hz, 2H), 3.67 (s, 3H), 5.07 (m, 2H), 5.86 (m, 1H), 7.29 (d, $J = 8.9$ Hz, 1H), 7.46 (d, $J = 8.7$ Hz, 1H), 7.74–7.79 (m, 2H), 8.02 (t, $J = 4.8$ Hz, 1H), 9.64 (s, 1H). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.22; H, 5.91; N, 9.04.

References and notes

1. Reiter, R. J. *Endocr. Rev.* **1991**, *12*, 151–180.
2. Cagnacci, A. *J. Pineal Res.* **1996**, *21*, 200–213.
3. Li, P.-K.; Witt-Enderby, P. A. *Drugs Future* **2000**, *25*, 945–957.
4. Miles, A.; Philbrick, D. R. S.; Thompson, C.; Melatonin, Clinical Perspectives. Oxford: Oxford University Press, 1988.
5. Tamarkin, L.; Baird, C. J.; Almeida, O. F. X. *Science* **1985**, *227*, 714–720.
6. Reppert, S. M.; Weaver, D. R.; Ebisawa, T. *Neuron* **1994**, *13*, 1177–1185.
7. Dubocovich, M. L.; Yun, K.; Al-Ghoul, W. M.; Benloucif, S.; Masana, M. I. *FASEB J.* **1998**, *12*, 1211–1220.
8. Ebisawa, T.; Karne, S.; Lerner, M.; Reppert, S. M. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 6133–6137.
9. Nosjean, O.; Ferro, M.; Coge, F.; Beauverger, P.; Henlin, J. M.; Lefoulon, F.; Fauchère, J. L.; Delagrange, P.; Canet, E.; Boutin, J. A. *J. Biol. Chem.* **2000**, *275*, 31311–31317.
10. Lotufo, C. M. C.; Lopes, C.; Dubocovich, M. L.; Farsky, S. H. P.; Markus, R. P. *Eur. J. Pharmacol.* **2001**, *430*, 351–357.
11. Pintor, J.; Martin, L.; Pelaez, T.; Hoyle, C. H. V.; Peral, A. *Eur. J. Pharmacol.* **2001**, *416*, 251–254.
12. Vella, F.; Ferry, G.; Delagrange, P.; Boutin, J. A. *Biochem. Pharmacol.* **2005**, *71*, 1–12.
13. Boutin, J. A.; Audinot, V.; Ferry, G.; Delagrange, P. *Trends Pharmacol. Sci.* **2005**, *26*, 412–419.
14. Pickering, D. S.; Niles, L. P. *Eur. J. Pharmacol.* **1990**, *175*, 71–77.
15. Molinari, E. J.; North, P.; Dubocovich, M. L. *Eur. J. Pharmacol.* **1996**, *301*, 159–168.
16. Leclerc, V.; Depreux, P.; Lesieur, D.; Caignard, D. H.; Renard, P.; Delagrange, P.; Guardiola-Lemaître, B.; Morgan, P. *J. Med. Chem.* **2002**, *45*, 1853–1859.
17. Boussard, M. F.; Truche, S.; Rousseau-Rojas, A.; Briss, S.; Descamps, S.; Droual, M.; Wierzbicki, M.; Ferry, G.; Audinot, V.; Delagrange, P.; Boutin, J. A. *Eur. J. Med. Chem.* **2006**, *41*, 306–320.
18. Depreux, P.; Lesieur, D.; Mansour, H. A.; Morgan, P.; Howell, H. E.; Renard, P.; Caignard, D.-H.; Pfeiffer, B.; Delagrange, P.; Guardiola, B.; Yous, S.; Demarque, A.; Adam, G.; Andrieux, J. *J. Med. Chem.* **1994**, *37*, 3231–3239.
19. Wallez, V.; Durieux-Poissonnier, S.; Chavatte, P.; Boutin, J. A.; Audinot, V.; Nicolas, J. P.; Bennejean, C.; Delagrange, P.; Renard, P.; Lesieur, D. *J. Med. Chem.* **2002**, *45*, 2788–2800.
20. Shah, B. L.; Desai, C. M. *J. Indian Chem. Soc.* **1984**, *61*, 651.
21. Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738.
22. Mailliet, F.; Ferry, G.; Vella, F.; Berger, S.; Cogé, F.; Chomarat, P.; Mallet, C.; Guénin, S. P.; Guillaumet, G.; Viaud-Massuard, M. C.; Yous, S.; Delagrange, D.; Boutin, J. A. *Biochem. Pharmacol.* **2005**, *71*, 74–88.