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(*R*)-2-(4-Phenylbutyl)dihydrobenzofuran derivatives as melatoninergic agents

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Abstract—(*R*)-2-(4-Phenylbutyl)dihydrobenzofuran derivatives (e.g., **3** and **4)** were synthesized as novel melatoninergic ligands with significantly lower vasoconstrictive activity in vitro in the rat tail artery. Binding affinity assays were performed on cloned human MT_1 and MT_2 receptors stably expressed in NIH3T3 cells.

Insomnia is the most common sleep disorder that affects 20–40% of American adults[1] with the incidence increasing significantly with age. Insomnia has a myriad of causes, one of which is disruption of the normal circadian sleep–wake cycle. Dysynchrony in the sleep–wake cycle can result from physiological changes. A therapeutic potential for the treatment of such disorders is resynchronization of the sleep–wake cycle via modulation of the melatoninergic system. The hormone melatonin (*N*-acetyl-5-methoxy-tryptamine) (Fig. 1) is synthesized and released primarily by the pineal gland in a circadian manner that closely follows the daily light/dark cycle.[2,3] It plays a central role in the regulation of circadian rhythms, the modulation of retinal physiology, and the control of seasonal cycles in vertebrates. In mammals, the precise role that melatonin plays in the coordination of circadian rhythms remains to be fully elucidated.[4] Melatonin alleviates jet lag, regulates delayed sleep phase syndrome,[5] and induces sleep.[6] In addition, melatonin has been shown to have antitumor properties and has been implicated in immune system responsiveness.[7] Many of the physiological effects of melatonin are mediated through G-protein-coupled receptors expressed primarily in the brain, retina, pituitary, and blood vessels.[8] Cloning of several G-protein-coupled melatonin receptor genes has revealed at least three distinct melatonin receptor subtypes. Two of these have been defined as

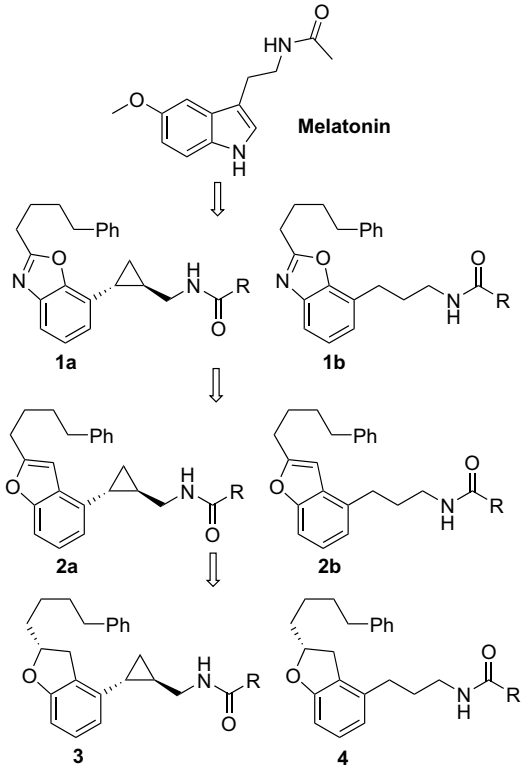

Figure 1.

Keywords: Melatonin; Melatonin receptors; Dihydrobenzofuran; Melatoninergic agents.
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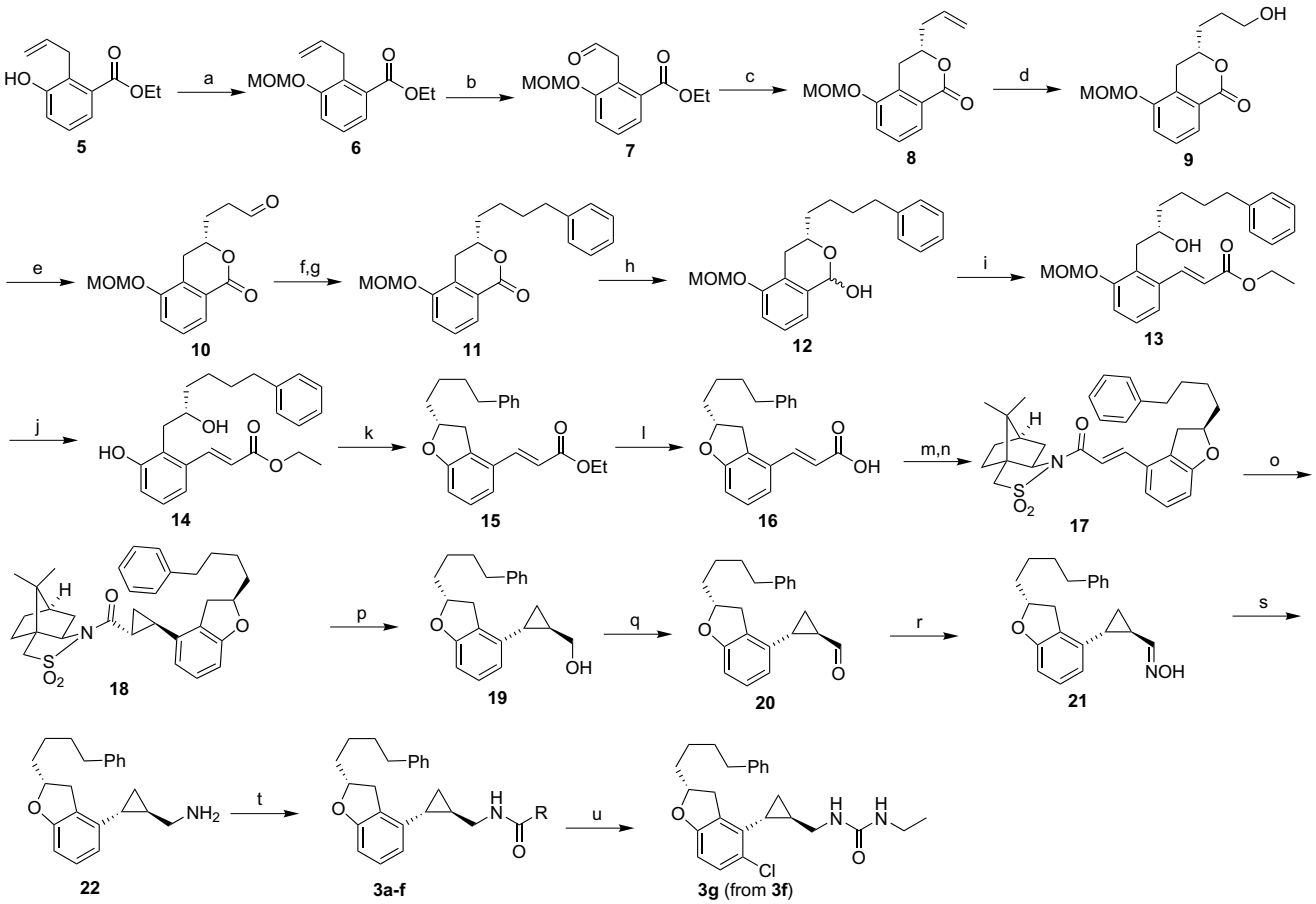
MT_1 and MT_2 and are found in mammals[9] while the third subtype, labeled MT_3, has recently been characterized as the hamster homologue of the human enzyme quinone reductase 2.[10]

We have recently reported the discovery of the benzoxazole nucleus as a novel melatoninergic pharmacophore.[11,12] Given the increased activity and selectivity of compounds incorporating a 4-phenylbutyl moiety at the 2-position of the benzoxazole heterocycle,[11,12] this substituent was retained in the context of an examination of potential substitutes for the benzoxazole scaffold. An initial study focused on the benzofuranyl moiety, which led to the identification of a novel series of potent, orally active melatonin receptor agonists exemplified by structure **2**.[13] Having established that the benzofuran moiety is a suitable bioisostere of benzoxazole, we further investigated this class of melatonin agonist by evaluating the effect of reduction of the furan ring. This transformation introduces a chiral center that would provide some insight into the role of absolute configuration at this site. However, for the initial study, the (*R*)-dihydrobenzofuran nucleus was selected based on a modeling hypothesis that predicted advantage for this absolute configuration.[14] As a result, (*R*)-2-(4-phenylbutyl)dihydrobenzofurans **3** and **4** were identified as novel and potent melatoninergic ligands. Herein we report the design, synthesis, and biological activity of this promising new series.

The compounds discussed in this report contain a (*R*)-2-(4-phenylbutyl)-2,3-dihydrobenzofuran nucleus and a general route to the first series of analogues, compounds **3a**–**g**, is described in Scheme 1. The phenol moiety of 2-allylphenol **5**[15] was protected as the MOM ether by treatment with MOMCl. The oxidative cleavage of the double bond of compound **6** under the standard literature conditions of OsO_4–$NaIO_4$[16] gave the desired aldehyde **7** in 74% yield. (*S*)-Lactone **8** was obtained by asymmetric alkylation of **7** in the manner of Brown[17] followed by in situ cyclization of the resulting homoallylic alcohol, which proceeded in good overall yield. Analysis of the product by HPLC using the Chiracel OJ (250×4.6 mm) column revealed an ee of 89.3%. Conclusive proof of the structure of **8** and the more advanced intermediate **18** were ultimately obtained by single crys-



Scheme 1. Reagents and conditions: (a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 96%; (b) OsO_4, $NaIO_4$, AcOEt, H_2O, rt, 74%; (c) (−)-*B*-methoxydiisopinocampheylborane, allylmagnesium bromide, ether, 80%; (d) BH_3·THF, THF, H_2O_2, NaOH, 75%; (e) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, 90%; (f) $BnPPh_3Br$, *n*-BuLi, THF, 86%; (g) 10% Pd/C, H_2, AcOEt, 99%; (h) DIBAL-H, PhMe, −78 °C, 99%; (i) Ph_3PCHCO_2Et, THF, reflux, 98%; (j) HCl, EtOH, rt, 100%; (k) Ph_3P, DEAD, THF, 0–25 °C, 95%; (l) NaOH, MeOH, H_2O, reflux, 96%; (m) $SOCl_2$, CH_2Cl_2, reflux; (n) (1*S*)-(−)-2,10-camphorsultam, NaH, PhMe, 0–25 °C, 92% (two steps); (o) CH_2N_2, $Pd(OAc)_2$, CH_2Cl_2, 0–25 °C, 76%; (p) LAH, THF, 0–25 °C, 93%; (q) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78–25 °C, 98%; (r) NH_2OH·HCl, NaOH, THF, reflux, 98%; (s) LAH, reflux, 84%; (t) R^1COCl, Et_3N, CH_2Cl_2 or R^2NCO, benzene; (u) NCS, MeCN, reflux.

tal X-ray analysis of the final derivative **3g**,[18] which is depicted in Figure 2. The alkene moiety of **8** was converted to terminal alcohol **9** by hydroboration with BH_3·THF followed by oxidation under standard conditions. Oxidation of the resulting alcohol under Swern conditions produced aldehyde **10**, which was subjected to Wittig olefination. Hydrogenation of the resulting olefin product in the presence of 10% Pd on charcoal as a catalyst gave compound **11**. DIBAL-H reduction of the lactone moiety of **11** furnished a mixture of diastereomeric lactols **12**, which was reacted with the stabilized ylide Ph_3PCHCO_2Et to give the α,β-unsaturated ester **13**. Deprotection of the MOM ether of **13** under acidic conditions furnished phenol **14**, which underwent ring closure to dihydrobenzofuran **15** with inversion of configuration at C-2 under the classical Mitsunobu conditions employing triphenylphosphine and diethyl azodicarboxylate (DEAD).[19] Hydrolysis of ester **15** under basic conditions afforded carboxylic acid **16**. Attention was then focused on completion of the synthesis by way of a chiral cyclopropanation. In the event, the chiral sultam auxiliary was appended by conversion of acid **16** to the acid chloride and treatment with the preformed sodium salt of (−)-camphorsultam.[15,20] A stereoselective, Pd-catalyzed cyclopropanation of the *N*-enoyl sultam **17** was accomplished by treatment with diazomethane.[15,20] Reductive removal of the sultam chiral auxiliary from **18** was achieved through treatment with LAH. Oxidation of the resultant alcohol **19** under standard Swern oxidation conditions provided aldehyde **20**. The next series of reactions involved converting the aldehyde functionality of **20** to the corresponding reverse amide or urea derivatives. In the event, aldehyde **20** was treated with NH_2OH to afford the corresponding oxime **21**. LAH reduction of **21** provided the primary amine **22**, which was acylated with a series of acid chlorides or reacted with ethyl isocyanate to produce amides **3a**–**e** and urea **3f**, respectively. The absolute stereochemistry of **3** was determined by X-ray diffraction analysis of the chlorinated analogue **3g** of the urea **3f**, obtained as depicted in Scheme 1. The structure is presented in Figure 2.

The dihydrobenzofuran derivatives **4a**–**f** incorporating a simple alkyl side chain were synthesized as shown in Scheme 2. Hydrogenation of the α,β-unsaturated ester **23** in the presence of 10% Pd on charcoal as a catalyst

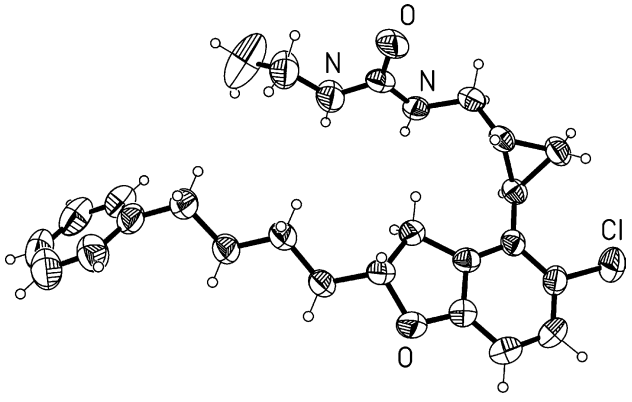
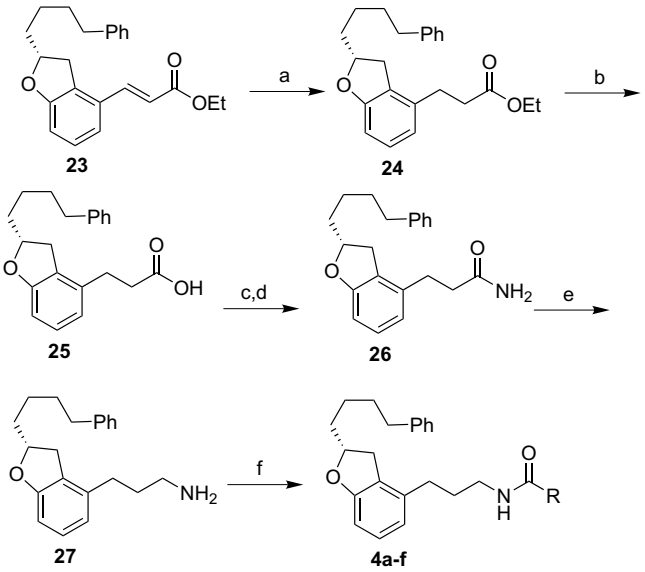


Figure 2. Thermal ellipsoid plot (35% ellipsoids) of crystalline **3g**.

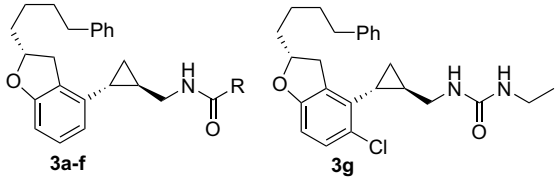


Scheme 2. Reagents and conditions: (a) H_2, 10% Pd/C, AcOEt, rt, 100%; (b) NaOH, MeOH, reflux, 99%; (c) $SOCl_2$, CH_2Cl_2, reflux; (d) NH_3, THF, −78–25 °C, 90% (two steps); (e) Red-Al, toluene, 0–25 °C, 94%; (f) R^1COCl, Et_3N, CH_2Cl_2 or R^2NCO, benzene.

gave compound **24**. Ester **24** was treated with NaOH to afford the corresponding acid which, in turn, was converted into amide **26** using $SOCl_2$ and NH_3. Red-Al-mediated reduction of **26** provided the primary amine **27**, which was acylated with a series of acid chlorides or reacted with ethyl isocyanate to produce the amides **4a**–**e** and urea **4f**, respectively.

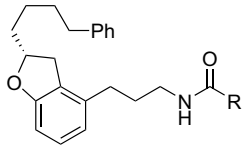
The K_i values for compounds **3** and **4** binding to human MT_1 and MT_2 melatonin receptor subtypes were determined in assays using 2-[^{125}I]-iodomelatonin according to the previously described assay method.[21,22] The chemical structures and associated K_i values are reported in Table 1. The MT_1 and MT_2 affinity values identified several compounds with excellent receptor affinity but most of the compounds exhibited little selectivity between MT_1 and MT_2 receptors. As seen in Table 1, (*R*)-2-(4-phenylbutyl)dihydrobenzofurans **3** exhibit high affinity for both human MT_1 and MT_2 melatonin receptors and are generally more potent ligands for both receptors than the corresponding benzofurans **2a**.[13] Within the cyclopropyl series, both the acetamide **3a** and propionamide **3b** demonstrate high MT_1 affinity with 2-fold lower affinity towards the MT_2 receptor. The binding affinity of these compounds to the MT_1 receptor shows some sensitivity to the identity of the *N*-acyl group with a range of 9-fold across the series of amides **3a**–**e**. The butyramide **3c** possessed excellent MT_1 and MT_2 binding affinity. The cyclopropanecarboxamide **3e** is somewhat exceptional compared to the corresponding benzofuran since it exhibited relatively higher MT_2 binding affinity. The isobutyramide **3d** and urea **3f** demonstrate good affinity for the MT_1 receptor but weaker MT_2 binding, parallel results to those seen with the benzofuran analogues.[13] However, the introduction of a chlorine atom on urea **3f** provided compound **3g**, which showed a further reduction in

Table 1. K_i of compounds **3a**–**g** and **4a**–**f** competing for the binding of 2-[^{125}I]-iodomelatonin to membrane preparations of NIH3T3 cells stably expressing human MT_1 or MT_2 melatonin receptor[21,22]



3a-f

3g



4a-f

Compd	R	MT_1 K_i (nM)	MT_2 K_i (nM)
Mel	—	0.3	0.7
3a	Me	**1**	2
3b	Et	1	2
3c	*n*Pr	2	2
3d	*i*Pr	6	90
3e	*c*Pr	1	5
3f	NHEt	9	40
3g	—	60	90
4a	Me	4	8
4b	Et	1	20
4c	*n*Pr	2	30
4d	*i*Pr	4	40
4e	*c*Pr	2	30
4f	NHEt	9	40

binding affinity at both receptors. Replacement of the conformationally constraining cyclopropane structural element of compounds **3a**–**f** by a more flexible alkyl side chain provided compounds **4a**–**f**, which demonstrated higher affinity for both MT_1 and MT_2 receptor subtypes than the previously reported corresponding compounds **2b**.[13] From this set of derivatives, only the acetamide **4a** demonstrated single digit nanomolar affinity for both MT_1 and MT_2 receptor subtypes. However, all of the other compounds, propionamide **4b**, butyramide **4c**, isobutyramide **4d**, cyclopropylcarboxamide **4e**, and urea **4f**, showed good affinity for the MT_1 receptor but were 5–20-fold weaker MT_2 ligands.

The two most active compounds to emerge from this series, **3a** and **3b**, were chosen for further evaluation in advanced profiling assays. It has been reported[23] that melatonin has a marked ability to enhance α-adrenoceptor-mediated vasoconstriction of the rat tail artery. Thus, the effect of these compounds on vascular smooth muscle was evaluated using the method already described.[24] Compared to melatonin, both **3a** and **3b** showed significantly reduced vasoconstrictive activity in assays conducted with rat caudal arteries (0.12 and 0.03 relative to melatonin, respectively).

In conclusion, the benzofuran scaffold substituted with the 4-phenylbutyl and alkylamide groups was successfully replaced by an isosteric dihydrobenzofuranyl moiety. This structural replacement led to the discovery of a series of (*R*)-2-(4-phenylbutyl)dihydrobenzofuran derivatives as more potent melatoninergic agents with significantly lower vasoconstrictive activity in vitro in the rat tail artery. The highlights of the synthesis are an asymmetric allylboration of an aldehyde containing an adjacent ester group and a stereoselective palladium-catalyzed cyclopropanation of an *N*-enoyl sultam. Intermediate **8** was exploited as the key precursor to a range of chiral 2-substituted dihydrobenzofuran derivatives in enantiopure form.

Acknowledgements

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